



US009181591B2

(12) **United States Patent**
Robins et al.

(10) **Patent No.:** US 9,181,591 B2
(45) **Date of Patent:** *Nov. 10, 2015

(54) **QUANTIFICATION OF ADAPTIVE IMMUNE CELL GENOMES IN A COMPLEX MIXTURE OF CELLS**

(71) Applicant: **Adaptive Biotechnologies Corporation**, Seattle, WA (US)

(72) Inventors: **Harlan S. Robins**, Seattle, WA (US); **Robert J. Livingston**, Seattle, WA (US)

(73) Assignee: **ADAPTIVE BIOTECHNOLOGIES CORPORATION**, Seattle, WA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **14/471,821**

(22) Filed: **Aug. 28, 2014**

(65) **Prior Publication Data**

US 2015/0051089 A1 Feb. 19, 2015

Related U.S. Application Data

(63) Continuation of application No. 14/199,167, filed on Mar. 6, 2014, which is a continuation of application No. 13/656,265, filed on Oct. 19, 2012.

(60) Provisional application No. 61/550,311, filed on Oct. 21, 2011.

(51) **Int. Cl.**
C12Q 1/68 (2006.01)

(52) **U.S. Cl.**
CPC **C12Q 1/6888** (2013.01); **C12Q 1/6881** (2013.01); **C12Q 1/686** (2013.01); **C12Q 2600/158** (2013.01); **C12Q 2600/16** (2013.01)

(58) **Field of Classification Search**

None

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,189,147 A	2/1993	Saito et al.
5,506,126 A	4/1996	Seed et al.
5,627,052 A	5/1997	Schrader
6,143,496 A	11/2000	Brown et al.
6,440,706 B1	8/2002	Vogelstein et al.
6,919,434 B1	7/2005	Goto et al.
7,148,040 B2	12/2006	Meagher et al.
7,741,463 B2	6/2010	Gormley et al.
7,785,783 B2	8/2010	Morley et al.
7,915,015 B2	3/2011	Vogelstein et al.
8,236,503 B2	8/2012	Faham et al.
8,507,205 B2	8/2013	Faham
8,628,927 B2	1/2014	Faham
8,691,510 B2	4/2014	Faham
8,748,103 B2	6/2014	Faham
8,795,970 B2	8/2014	Faham
2002/0110807 A1	8/2002	Pilarski et al.
2003/0120061 A1	6/2003	Zhang

2005/0255482 A1	11/2005	Morley et al.
2006/0228350 A1	10/2006	Wu et al.
2006/0233812 A1	10/2006	Burnie et al.
2006/0234234 A1	10/2006	Van Dongen et al.
2007/0020670 A1	1/2007	Loken et al.
2007/0117134 A1	5/2007	Kou
2007/0243564 A1	10/2007	Lawson et al.
2008/0069770 A1	3/2008	Hercend et al.
2008/0166704 A1	7/2008	Marche et al.
2009/0208955 A1 *	8/2009	Robins et al. 435/6
2010/0021896 A1 *	1/2010	Han 435/6
2010/0027896 A1	2/2010	Geva et al.
2010/0151471 A1 *	6/2010	Faham et al. 435/6
2010/0159456 A1	6/2010	Albitar
2010/0167353 A1	7/2010	Walder et al.
2010/0330571 A1	12/2010	Robins et al.
2011/0003291 A1	1/2011	Pasqual et al.
2011/0014659 A1 *	1/2011	Balazs et al. 435/91.2
2011/0129830 A1	6/2011	Ladner et al.
2011/0207134 A1 *	8/2011	Faham et al. 435/6.11
2011/0207135 A1 *	8/2011	Faham et al. 435/6.11
2012/0058902 A1 *	3/2012	Livingston et al. 506/7
2012/0135409 A1	5/2012	Faham
2012/0220466 A1 *	8/2012	Fire et al. 506/2
2013/0005584 A1	1/2013	Faham
2013/0065768 A1	3/2013	Zheng
2013/0150252 A1	6/2013	Faham

(Continued)

FOREIGN PATENT DOCUMENTS

EP	2062982 A1	5/2009
EP	2088432 A1	8/2009

(Continued)

OTHER PUBLICATIONS

Robins et al. (Comprehensive assessment of T-cell receptor β-chain diversity in αβ T cells, Blood, vol. 114, No. 19, Nov. 5, 2009).*

Boyd et al. (Measurement and Clinical Monitoring of Human Lymphocyte Clonality by Massively Parallel V-D-J Pyrosequencing, Sci Transl Med. Dec. 23, 2009;1(12):12ra23).*

Boyd et al. (Individual Variation in the Germline Ig Gene Repertoire Inferred from Variable Region Gene Rearrangements, J Immunol. Jun. 15, 2010;184(12):6986-92).*

(Continued)

Primary Examiner — Stephanie K Mummert

Assistant Examiner — Aaron Priest

(74) *Attorney, Agent, or Firm* — Cooley LLP

(57) **ABSTRACT**

Compositions and methods are described for highly sensitive quantification of the relative representation of DNA from adaptive immune cells (e.g., T and/or B lymphocytes) in DNA extracted from complex mixtures of cells that include cells which are not adaptive immune cells. Included are methods for determining the relative presence in a tumor of tumor infiltrating lymphocytes (TIL), the relative presence of lymphocytes infiltrating a somatic tissue that is the target of an autoimmune disease, and the relative presence of lymphocytes infiltrating a transplanted organ.

(56)

References Cited**U.S. PATENT DOCUMENTS**

2013/0196328	A1	8/2013	Pepin
2013/0202718	A1	8/2013	Pepin
2013/0236895	A1	9/2013	Faham
2013/0253842	A1	9/2013	Sherwood et al.
2013/0267427	A1	10/2013	Faham
2013/0288237	A1	10/2013	Robins et al.
2013/0302801	A1	11/2013	Asbury
2013/0344066	A1	12/2013	Faham
2014/0057799	A1	2/2014	Johnson et al.
2014/0155277	A1	6/2014	Wiley
2014/0186848	A1	7/2014	Robins et al.
2014/0194295	A1	7/2014	Robins et al.
2014/0206548	A1	7/2014	Robins et al.
2014/0206549	A1	7/2014	Robins et al.
2014/0213463	A1	7/2014	Robins et al.
2014/0221220	A1	8/2014	Robins et al.
2014/0234835	A1	8/2014	Pepin
2014/0235454	A1	8/2014	Faham
2014/0255929	A1	9/2014	Zheng
2014/0255944	A1	9/2014	Carlton
2014/0256567	A1	9/2014	Robins et al.
2014/0256592	A1	9/2014	Faham
2014/0322716	A1	10/2014	Robins et al.
2015/0017652	A1	1/2015	Robins et al.
2015/0031555	A1	1/2015	Johnson et al.

FOREIGN PATENT DOCUMENTS

JP	2006-501842	A	1/2006
JP	2007-515955	A	6/2007
WO	WO 97/13877	A1	4/1997
WO	WO 2006/110855	A2	10/2006
WO	WO 2006/138284	A2	12/2006
WO	WO 2009/095567	A2	8/2009
WO	WO 2010/053857	A2	5/2010
WO	WO 2010/151416	A1	12/2010
WO	WO 2011/06738	A2 *	9/2011
WO	WO 2011/139371	A1	11/2011
WO	WO 2012/027503	A2	3/2012
WO	WO 2012/083069	A2	6/2012
WO	WO 2012/083225	A2	6/2012
WO	WO 2013/134302	A1	9/2012
WO	WO 2013/059725	A1	4/2013
WO	WO 2013/086450	A1	6/2013
WO	WO 2013/134162	A2	9/2013
WO	WO 2013/155119	A1	10/2013
WO	WO 2013/158936	A1	10/2013
WO	WO 2013/181428	A2	12/2013
WO	WO 2013/188471	A2	12/2013
WO	WO 2014/018460	A1	1/2014
WO	WO 2014/026031	A1	2/2014
WO	WO 2014/062945	A1	4/2014
WO	WO 2014/062959	A1	4/2014
WO	WO 2014/066184	A1	5/2014
WO	WO 2014/130685	A1	8/2014

OTHER PUBLICATIONS

- Faham et al. (Deep-sequencing approach for minimal residual disease detection in acute lymphoblastic leukemia, *Blood*. Dec. 20, 2012; 120(26): 5173-5180).*
- Logan et al. (High-throughput VDJ sequencing for quantification of minimal residual disease in chronic lymphocytic leukemia and immune reconstitution assessment, *Proc Natl Acad Sci U S A*. Dec. 27, 2011;108(52):21194-9).*
- Wu et al. (High-throughput immunoglobulin repertoire analysis distinguishes between human IgM memory and switched memory B-cell populations, *Blood*, Aug. 19, 2010, vol. 116, No. 7).*
- Sherwood et al (Deep Sequencing of the Human TCR α and TCR β Repertoires Suggests that TCR β Rearranges After ab and gd T Cell Commitment, *Sci Transl Med*. Jul. 6, 2011;3(90):90ra61).*
- Robins et al. (Overlap and Effective Size of the Human CD8+ T Cell Receptor Repertoire, *Sci Transl Med*. Sep. 1, 2010;2(47):47ra64).*
- Robins (Detecting and monitoring lymphoma with high-throughput sequencing, *Oncotarget* 2011; 2: 287-288).*
- Klarenbeek et al. (Human T-cell memory consists mainly of unexpanded clones, *Immunology Letters* 133 (2010) 42-48).*
- Freeman et al. (Profiling the T-cell receptor beta-chain repertoire by massively parallel sequencing, *Genome Res*. Oct. 2009;19(10):1817-24).*
- Robins (The Computational Detection of Functional Nucleotide Sequence Motifs in the Coding Regions of Organisms, *Exp Biol Med* (Maywood). Jun. 2008;233(6):665-73).*
- Akatsuka Y. et al., "Rapid screening of T-cell receptor (TCR) variable gene usage by multiplex PCR: Application for assessment of clonal composition", *Tissue Antigens*, 53:122-134 (1999).
- Al-Lazikani, B. et al., "Standard Conformations for the Canonical Structures of Immunoglobulins," *J. Mol. Biol.*, 273:927-948 (1997).
- Alexandre, D. et al. "H. sapiens rearranged T-cell receptor gamma chain gene, V2-JP1", GenBank accession No: X57737, NCBI, Nov. 14, 2006, 8 pages [online] [retrieved on Jun. 26, 2013] Retrieved from the Internet <URL:<http://www.ncbi.nlm.nih.gov/nuccore/x57737>>.
- Alexandre, D. et al. "H. sapiens rearranged T-cell receptor gamma chain gene, V3RS-J1 (hybrid joint)", GenBank accession No: X57740, NCBI, Feb. 11, 1997, 8 pages [online] [retrieved on Jun. 26, 2013] Retrieved from the internal <URL:<http://www.ncbi.nlm.nih.gov/nuccore/x57740>>.
- Arstila, T.P. et al., "A direct estimate of the human $\alpha\beta$ T cell receptor diversity," *Science*, 286(5441):958-961 (1999).
- Bahloul, M. et al., "Clinical impact of molecular diagnostics in low-grade lymphoma," *Best Practice & Research Clinical Haematology*, 18(1):97-111 (2005).
- Benichou, J. et al., "Rep-Seq: uncovering the immunological repertoire through next-generation sequencing", *Immunology*, 135(3):183-191 (2012).
- Bernardin, F. et al., "Estimate of the total number of CD8+ clonal expansions in healthy adults using a new DNA heteroduplex-tracking assay for CDR3 repertoire analysis", *Journal of Immunological Methods*, 274(1-2):159-175 (2003).
- Berquam-Vrieze, K. et al., "Cell of origin strongly influences genetic selection in a mouse model of T-ALL", *Blood*, 118:4646-4656 (2011).
- Blow, N., "PCR's next frontier," *Nature Methods*, 4(10):869-875 (2007).
- Bolotin, D.A. et al., "Next generation sequencing for TCR repertoire profiling: Platform-specific features and correction algorithms", *Eur. J. Immunol.*, 42:3073-3083 (2012).
- Bonarius, H.P.J. et al., "Monitoring the T-Cell Receptor Repertoire at Single-Clone Resolution", *PLOS One*, 1(e55):1-10 (2006).
- Bradfield, S.M. et al., "Graft-versus-leukemia effect in acute lymphoblastic leukemia: the importance of tumor burden and early detection," *Leukemia*, 18:1156-1158 (2004).
- Brenan, C. et al., "High throughput, nanoliter quantitative PCR," *Drug Discovery Today: Technologies*, 2(3):247-253 (2005).
- Buck, G.A. et al., "Design Strategies and Performance of Custom DNA Sequencing Primers", *Biotechniques*, 27(3):528-536 (1999).
- Butkus, B., "Hutch Team Uses ddPCR to Quantify T-Cell Response in Tumors; Adaptive Biotech Eyes Market", *PCR Insider*, Dec. 12, 2013, 3 pages <http://www.genomeweb.com/print/1323296>.
- Campana, D., "Progress of Minimal Residual Disease Studies in Childhood Acute Leukemia," *Curr Hematol Malig Rep*, 5:169-176 (2010).
- Caporaso, J.G. et al., "Global patterns of 16S rRNA diversity at a depth of millions, of sequences per sample", *PNAS*, 108(Suppl. 1):4516-4522 (2010).
- Carlson, C.S. et al., "Using synthetic templates to design an unbiased multiplex PCR assay", *Nature Communications*, 4:2680, pp. 1-9 (2013).
- Cavé, H. et al., "Clinical Significance of minimal residual disease in childhood acute lymphoblastic leukemia," *The New England Journal of Medicine*, 339:591-598 (1998).
- Chen, Y. et al., "T-cell receptor gene expression in tumour-infiltrating lymphocytes and peripheral blood lymphocytes of patients with nasopharyngeal carcinoma", *British Journal of Cancer*, 72(1):117-22 (1995).
- Chothia, C. et al., "Canonical structures for the hypervariable regions of immunoglobulins," *J. Mol. Biol.*, 196:901-917, Abstract only (1987).

(56)

References Cited**OTHER PUBLICATIONS**

- Chothia, C. et al., "Conformations of immunoglobulin hypervariable regions," *Nature*, 342:877-883 (1989).
- Ciudad, J. et al., "Detection of abnormalities in B-cell differentiation pattern is a useful tool to predict relapse in precursor-B-ALL," *British Journal of Haematology*, 104:695-705 (1999).
- Coustan-Smith, E. et al., "Clinical importance of minimal residual disease in childhood acute lymphoblastic leukemia," *Blood*, 96(8):2691-2696 (2000).
- Coustan-Smith, E. et al., "Early T-cell precursor leukaemia: a subtype of very high-risk acute lymphoblastic leukaemia," *Lancet Oncology*, 10:147-156 (2009).
- Coustan-Smith, E. et al., "Prognostic importance of measuring early clearance of leukemic cells by flow cytometry in childhood acute lymphoblastic leukemia", *Blood*, 100(1):52-58 (2002).
- Curran-Everett, D., "Multiple comparisons: philosophies and illustrations", *Am J Physiol Regulatory Integrative Comp Physiol.*, 279:R1-R8 (2000).
- Dash, P. et al., "Paired analysis of TCR[alpha] and TCR[beta] chains at the single-cell level in mice", *Journal of Clinical Investigation*, 121(1):288-295 (2011).
- De Jonge, H.J.M., et al., "Evidence Based Selection of Housekeeping Genes," *PLoS One*, 9(e989):1-5.(2007).
- DeNucci, C.C. et al., "Integrin function in T-cell homing to lymphoid and nonlymphoid sites: getting there and staying there," *Critical Reviews in Immunology*, 29(2):87-109 (2009).
- Dheda, K., et al., "Validation of housekeeping genes for normalizing RNA expression in real-time PCR," *Bio Techniques*, 37:112-119 (2004).
- Dik, W., et al. "New insights on human T cell development by quantitative T cell receptor gene rearrangement studies and gene expression profiling," *JEM*, 201(11):1715-1723 (2005).
- Dobosy, J. et al., "RNase H-dependent PCR (rhPCR): improved specificity and single nucleotide polymorphism detection using blocked cleavable primers," *BMC Biotechnology*, 11(80):1-18 (2011).
- Droese, J., et al., "Validation of BIOMED-2 multiplex PCR tubes for detection of TCRB gene rearrangements in T-cell malignancies," *Leukemia*, 18:1531-1538 (2004).
- Duby, A.U. et al., "Human T-cell receptor aberrantly rearranged beta-chain J1.5-Dx-J2.1 gene," *PNAS*, GenBank accession No. M13574.1, bases 1 to 100, 4 pages (1986).
- Edwards and Gibbs, "Multiplex PCR: advantages, development, and applications," *Genome Research*, 3:S65-S75 (1994).
- Elinfiro, E.M., et al., "Multiplex PCR: Optimization and Application in Diagnostic Virology", *Clinical Microbiology Reviews*, 13(4):559-570 (2000).
- Emerson, R.O. et al., "High-throughput sequencing of T-cell receptors reveals a homogeneous repertoire of tumour-infiltrating lymphocytes in ovarian cancer", *Journal of Pathology*, 231:433-440 (2013).
- Flohr, T., et al., "Minimal residual disease-directed risk stratification using real-time quantitative PCT analysis of immunoglobulin and T-cell receptor gene rearrangements in the international multicenter trial AIEOP-BFM ALL 2000 for childhood acute lymphoblastic leukemia", *Leukemia*, 22:771-782 (2008).
- Gerlinger, M. et al., "Ultra deep T cell receptor sequencing reveals the complexity and intratumour heterogeneity of T cell clones in renal cell carcinomas", *Journal of Pathology*, 231:424-432 (2013).
- Gonzalez, S.F. et al., "Trafficking of B Cell Antigen in Lymph Nodes," *Ann. Rev. Immunol.*, 29:215-233 (2011).
- Henegariu, O. et al., "Multiplex PCR: Critical Parameters and Step-By-Step Protocol," *Biotechniques*, Informa HealthCare, 23(3):504-511 (1997).
- Hodges, E. et al., "Diagnostic role of tests for T cell receptor (TCR) genes", *J Clin Pathol.*, 56(1):1-11 2003).
- Hwang, H.Y. et al., "Identification of a Commonly used CDR3 Region of Infiltrating T Cells Expressing V β 13 and V β 15 Derived from Psoriasis Patients", *The Journal of Investigative Dermatology*, 120(3):359-384 (2003).
- Jochems and Schlom, "Tumor-infiltrating immune cells and prognosis: the potential link between conventional cancer therapy and immunity," *Experimental Biology and Medicine*, 236:567-579 (2011).
- Kalinina, O. et al., "Nanoliter scale PCT with TaqMan detection," *Nucleic Acids Research*, 25(10):1999-2004 (1997).
- Kalos, M. et al., "T Cells with Chimeric Antigen Receptors Have Potent Antitumor Effects and Can Establish Memory in Patients with Advanced Leukemia", *Science Translational Medicine*, 3(95ra73):1-11 (2011).
- Kaplinski and Remm, "MultiPLX Automatic Grouping and Evaluation of PCR Primers", *Methods in Molecular Biology*, 402(PCR Primer Design):287-303 (2004).
- Katz, S.C. et al., "T Cell Infiltrate Predicts Long-Term Survival Following Resection of Colorectal Cancer Liver Metastases," *Ann. Surg. Oncol.*, 16:2524-2530 (2009).
- Kehrl, J.H. et al., "Chemoattractant Receptor Signaling and Its Role in Lymphocyte Motility and Trafficking," *Current Topics in Microbiology and Immunology*, 334:107-127 (2009).
- Kiianitsa, et al., "Development of Tools for T-Cell Repertoire Analysis (TCRB Spectratyping) for the Canine Model of Hematopoietic Cell Transplantation", *Blood*, ASH—Annual Meeting Abstracts, 110:Abstract 4873, 2 pages (2007).
- Kneba, M., et al., "Analysis of Rearranged T-cell Receptor β -Chain Genes by Polymerase Chain Reaction (PCR) DNA Sequencing and Automated High Resolution PCR Fragment Analysis", *Blood*, 86:3930-3937 (1995).
- Ladányi, A., et al., "Prognostic impact of β -cell density in cutaneous melanoma", *Cancer Immunol. Immunother.*, 60(12):1729-1738 (2011).
- Larimore, K., et al., "Shaping of Human Germline IgH Repertoires Revealed by Deep Sequencing," *The Journal of Immunology*, 189(6):3221-3230 (2012).
- Ladetto, M. et al., "Real-Time Polymerase Chain Reaction of Immunoglobulin Rearrangements for Quantitative Evaluation of Minimal Residual Disease in Multiple Myeloma", *American Society for Blood and Marrow Transplantation*, 6(3):241-253 (2000).
- Ladetto, M. et al., "Real-time polymerase chain reaction in multiple myeloma: Quantitative analysis of tumor contamination of stem cell harvests", *Experimental Hematology*, 30:529-536 (2002).
- Lowe, T., et al., "A computer program for selection of oligonucleotide primers for polymerase chain reactions," *Nucleic Acids Research*, 18(7):1757-1761 (1990).
- Lúcio, P. et al., "Flow cytometric analysis of normal B cell differentiation: a frame of reference for the detection of minimal residual disease in precursor-B-ALL", *Leukemia*, 13:419-427 (1999).
- Mahmoud, S.M.A. et al., "Tumor-Infiltrating CD8+ Lymphocytes Predict Clinical Outcome in Breast Cancer", *Journal of Clinical Oncology*, 29(15):1949-1955 (2011).
- Marelli-Berg, F.M., et al., "Memory T-cell trafficking: new directions for busy commuters," *Immunology*, 130:158-165 (2010).
- Mariani, S. et al., "Comprehensive assessment of the TCRBV repertoire in small T-cell samples by means of an improved and convenient multiplex PCR method," *Experimental Hematology*, 37(6):728-738 (2009).
- Markoulatos, P. et al., "Multiplex Polymerase Chain Reaction: A Practical Approach", *Journal of Clinical Laboratory Analysis*, 16:47-51 (2002).
- Maryanski, J.L. et al., "A quantitative, single-cell PCR analysis of an antigen-specific TCR repertoire 8 selected during an in vivo CD8 response: direct evidence for a wide range of clone sizes with uniform tissue distribution", *Molecular Immunology*, 36:745-753 (1999).
- Maślanka, K. et al., "Molecular Analysis of T-Cell Repertoires: Spectratypes Generated by Multiplex Polymerase Chain Reaction and Evaluated by Radioactivity or Fluorescence", *Human Technology*, 44(1):28-34 (1995).
- Merriam-Webster, 4 pages (definition of "substantial," accessed Apr. 25, 2014).
- Merriam-Webster, 2 pages (definition of "e.g.," accessed Apr. 25, 2014).
- Miqueu, P. et al., "Statistical analysis of CDR3 length distributions for the assessment of T and B cell repertoire biases," *Molecular Immunology*, 44:1057-1064 (2007).

(56)

References Cited**OTHER PUBLICATIONS**

- Monod, M.Y. et al., "IMGT/JunctionAnalysis: the first tool for the analysis of the immunoglobulin and T cell receptor complex V-J and V-D-J JUNCTIONS", *Bioinformatics*, 20(Suppl 1):i379-385 (2004).
- Slichtom, J.L. et al., "Homo sapiens germline beta T-cell receptor locus," NCBI Accession No. L36092 NCBI, 254 pages (2009) Retrieved from the Internet: <URL:<http://www.ncbi.nlm.nih.gov/nuccore/L36092>>.
- Nicot, N. et al., "Housekeeping gene selection for real-time RT-PCR normalization in potato during biotic and abiotic stress," *Journal of Experimental Botany*, 56(421):2907-2914 (2005).
- Nolan, T. et al., "Quantification of mRNA using real-time RT-PCR," *Nature Protocols*, 1(3):1559-1582 (2006).
- PCT International Search Report and Written Opinion, PCT/US2010/021264, mailed Apr. 14, 2010, 7 pages.
- PCT International Preliminary Report on Patentability, PCT/US2010/021264, mailed Jul. 19, 2011, 5 pages.
- PCT International Search Report and Written Opinion, PCT/US2013/040221, mailed Sep. 23, 2013, 15 Pages.
- PCT International Preliminary Report on Patentability, PCT/US2013/040221, dated Apr. 24, 2014, 41 pages.
- PCT International Search Report and Written Opinion, PCT/US2010/037477, mailed Sep. 24, 2010, 10 pages.
- PCT International Preliminary Report on Patentability, PCT/US2010/037477, dated Jan. 4, 2012, 7 pages.
- PCT International Search Report and Written Opinion, PCT/US2012/061193, mailed Mar. 28, 2013, 13 pages.
- PCT International Preliminary Report on Patentability, PCT/US2012/061193, mailed Apr. 22, 2014, 8 pages.
- PCT International Search Report and Written Opinion, PCT/US2012/068617, mailed Mar. 28, 2013, 10 pages.
- PCT International Preliminary Report on Patentability, PCT/US2012/068617, mailed Jun. 10, 2014, 6 pages.
- PCT International Search Report and Written Opinion, PCT/US2013/062925, mailed Nov. 25, 2013, 12 pages.
- PCT Second Written Opinion for PCT/US2013/062925 mailed Jan. 23, 2015, 7 pages.
- PCT International Search Report and Written Opinion, PCT/US2011/049012, mailed Apr. 10, 2012, 9 pages.
- PCT International Preliminary Report on Patentability, PCT/US2011/049012, dated Feb. 26, 2013, 5 pages.
- PCT International Search Report and Written Opinion, PCT/US2013/045994, mailed Oct. 25, 2013, 15 pages.
- PCT International Preliminary Report on Patentability, PCT/US2013/045994, dated Dec. 16, 2014, 10 pages.
- PCT International Search Report and Written Opinion, PCT/US2011/026373, mailed Oct. 20, 2011, 17 pages.
- PCT International Preliminary Report on Patentability, PCT/US2011/026373, dated Aug. 28, 2012, 11 pages.
- PCT International Search Report and Written Opinion, PCT/US2014/030859, mailed Jul. 18, 2014, 7 pages.
- Pekin, D. et al., "Quantitative and sensitive detection of rare mutations using droplet-based microfluidics", *Lab Chip*, 11(3):2156 (2011).
- Perkel, J., "Overcoming the Challenges of Multiplex PCR," Biocompare Editorial Article, Oct. 23, 2012, 6 Pages, can be retrieved at URL:<http://www.biocompare.com/Editorial-Articles/117895-Multiplex-PCR/>.
- Pohl, G. and Shih, "Principle and applications of digital PCR," *Expert Rev. Mol. Diagn.*, 4(1):41-47 (2004).
- Puisieux, I. et al., "Oligoclonality of Tumor-Infiltrating Lymphocytes from Human Melanomas," *The Journal of Immunology*, 153:2807-2818 (1994).
- Rasmussen, T. et al., Quantitation of minimal residual disease in multiple myeloma using an allele-specific real-time PCR assay, *Experimental Hematology*, 28:1039-1045 (2000).
- Reischl and Kochanowski, at al., "Quantitative PCR a Survey of the Present Technology," *Molecular Biotechnology*, 3:55-71 (1995).
- Robins, H.S. et al., "Digital Genomic Quantification of Tumor Infiltrating Lymphocytes", *Science Translational Medicine*, 5:214ra169, 19 pages, Supplementary Materials (2013).
- Robins, H., et al., "Ultra-sensitive detection of rare T cell clones", *Journal of Immunological Methods*, 375:14-19 (2012).
- Rock, E.P. et al., "CDR3 Length in Antigen-specific Immune Receptors", *J. Exp. Med.*, 179:323-328 (1994).
- Rosenberg, S.A. et al., "New Approach to the Adoptive Immunotherapy of Cancer with Tumor-Infiltrating Lymphocytes", *Science*, 233(4770):1318-1321 (1986).
- Rosenthal, M. et al., "Immaturity Associated Antigens Are Lost During Induction for T Cell Lymphoblastic Leukemia: Implications for Minimal Residual Disease Detection", *Cytometry Part B (Clinical Cytometry)*, 78:139-146 (2010).
- Rozen, S., et al., "Primer3 on the WWW for General Users and for Biologist Programmers," *Methods in Molecular Biology*, Bioinformatics Methods and Protocols, 132:365-386 (2000).
- Saada, R. et al., "Models for antigen receptor gene rearrangement: CDR3 length", *Immunology and Cell Biology*, 85:323-332 (2007).
- Santalucia, Jr., J., "Physical Principles and Visual-OMP Software for Optimal PCR Design," *Methods in Molecular Biology*, 402(PCR Primer Design):3-33, 40 pages (2007).
- Santamaria, P. et al., "Beta-Cell-Cytotoxic CDS T Cells from Nonobese Diabetic Mice Use Highly Homologous T Cell Receptor α-Chain CDR3 Sequences", *The Journal of Immunology*, 154(5):2494-2503 (1995).
- Schlissel, M.S. et al., "Leukemia and lymphoma: a cost of doing business for adaptive immunity", *Genes Dev.*, 20(12):1539-1544 (2006).
- Schrappe, M. et al., "Late MRD response determines relapse risk overall and in subsets of childhood T-cell ALL: results of the AIEOP-BFM-ALL 2000 study", *Blood*, 118(8):2077-2084 (2011).
- Silver, N. et al., "Selection of housekeeping genes for gene expression studies in human reticulocytes using real-time PCR", *BMC Molecular Biology*, 7(33):1-9 (2006).
- Sint, D., et al., "Advances in multiplex PCR: balancing primer efficiencies and improving detection success," *Methods in Ecology and Evolution*, 3(5):898-905 (2012).
- Standard Sequencing Primers, Max Planck Genome Center Cologne, Jan. 15, 2011, downloaded from <https://genomeweb.mpiipg.mpg.de/SeqOrderDB/export/sequencing-primers.html>.
- Stein and Nombela-Arrieta, "Chemokine control of lymphocyte trafficking: a general overview," *Immunology*, 116(10):1-12 (2005).
- Steinmetz, O.M. et al., "Chemokines and B cells in renal inflammation and allograft rejection," *Frontiers in Bioscience* (Schol. Ed.), 1:13-22 (2009).
- Straten, Per thor et al., "T-cell clonotypes in cancer", *Journal of Translational Medicine*, 2(1):11 (2004).
- Supplementary European Search Report for European Application No. 10732172.1, dated May 29, 2012, 5 pages.
- Szczepanski, T. et al., "Minimal residual disease in leukemia patients", *Lancet Oncology*, 2:409-417 (2001).
- Tewhey, R. et al., "Corrigendum: Microdroplet-based PCR enrichment for large-scale targeted sequencing", *Nature Biotechnology*, 28(2):178, 1 page (2010).
- Tewhey, R. et al., "Microdroplet-based PCR enrichment for large-scale targeted sequencing," *Nature Biotechnology*, 27(11):1025-1031 (2009).
- Triebel, F. et al., "A Unique V-J-C-Rearranged Gene Encodes A γ Protein Expressed on the Majority of CD3+ T Cell Receptor α/β Circulating Lymphocytes", *J. Exp. Med.*, 167:694-699 (1988).
- Van Der Velden, V.H.J. et al., "Analysis of minimal residual disease by Ig/TCR gene rearrangements: guidelines for interpretation of real-time quantitative PCR data," *Leukemia*, 21:604-611 (2007).
- Van Der Velden, V.H.J. et al., "Optimization of PCR-based minimal residual disease diagnostics for childhood acute lymphoblastic leukemia in a multi-center setting," *Leukemia*, 21:706-713 (2007).
- Van Der Velden, V.H.J., et al., "Detection of minimal residual disease in hematologic malignancies by realtime quantitative PCR: principles, approaches, and laboratory aspects," *Leukemia*, 17:1013-1034 (2003).
- Van Der Velden, V.H.J., et al., "Real-time quantitative PCR for detection of minimal residual disease before allogeneic stem cell trans-

(56)

References Cited**OTHER PUBLICATIONS**

- plantation predicts outcome in children with acute lymphoblastic leukemia”, *Leukemia*, 15:1485-1487 (2001).
- Van Dongen, J.J.M. et al., “Design and standardization of PCR primers and protocols for detection of clonal immunoglobulin and T-cell receptor gene recombinations in suspect lymphoproliferations: Report of the BIOMED-2 Concerted Action BMHC-CT98-3936”, *Leukemia*, 17:2257-2317 (2003).
- Van Dongen, J.J.M. et al., “Prognostic value of minimal residual disease in acute lymphoblastic leukaemia in childhood,” *The Lancet*, 352:1731-1738 (1998).
- Venturi, V. et al., “The molecular basis for public T-cell responses?” *Nature Reviews*, 8:231-238 (2008).
- Venturi, V. et al., “TCR β-Chain Sharing in Human CD8+ T Cell Responses to Cytomegalovirus and EBV^{1*}”, *The Journal of Immunology*, 181:7853-7862 (2008).
- Verhagen, O.J.H.M., et al., “Application of germline IGH probes in real-time quantitative PCR for the detection of minimal residual disease in acute lymphoblastic leukemia,” *Leukemia*, 14:1426-1435 (2000).
- Volgelstein and Kinzler, “Digital PCR,” *Genetics*, PNAS, 96:9236-9241 (1999).
- Wang, X. et al., “Quantitative Measurement of Pathogen Specific Human Memory T Cell Repertoire Diversity using a CDR3 B-Specific Microarray”, *BMC Genomics*, 8(329): 1-13 (2007).
- Ward and Marelli-Berg, “Mechanisms of chemokine and antigen-dependent T-lymphocyte navigation,” *Biochem. J.*, 418:13-27 (2009).
- Weinstein, J.A. et al., “High-Throughput Sequencing of the Zebrafish Antibody Repertoire”, *Science*, 324:807-810 (2009).
- Wood, B., “9-Color and 10-Color Flow Cytometry in the Clinical Laboratory,” *Arch Pathol Lab Med*, 130:680-690 (2006).
- Wu, H.D. et al., “The Lymphocytic Infiltration in Calcific Aortic Stenosis Predominantly Consists of Clonally Expanded T Cells”, *The Journal of Immunology*, 178(8):5329-5339 (2007).
- Xu, W. et al., “A Novel Universal Primer-Multiplex-PCR Method with Sequencing Gel Electrophoresis Analysis,” *PLoS One*, 7(1):e22900, pp. 1-10 (2012).
- Yassai, M.B. et al., “A clonotype nomenclature for T cell receptors”, *Immunogenetics*, 61:493-502 (2009).
- Zhong, Q. et al., “Multiplex digital PCR: breaking the one target per color barrier of quantitative PCR”, *Lab Chip*, 11:2167-2174 (2011). US 8,642,750, 02/2014, Faham et al. (withdrawn)

* cited by examiner

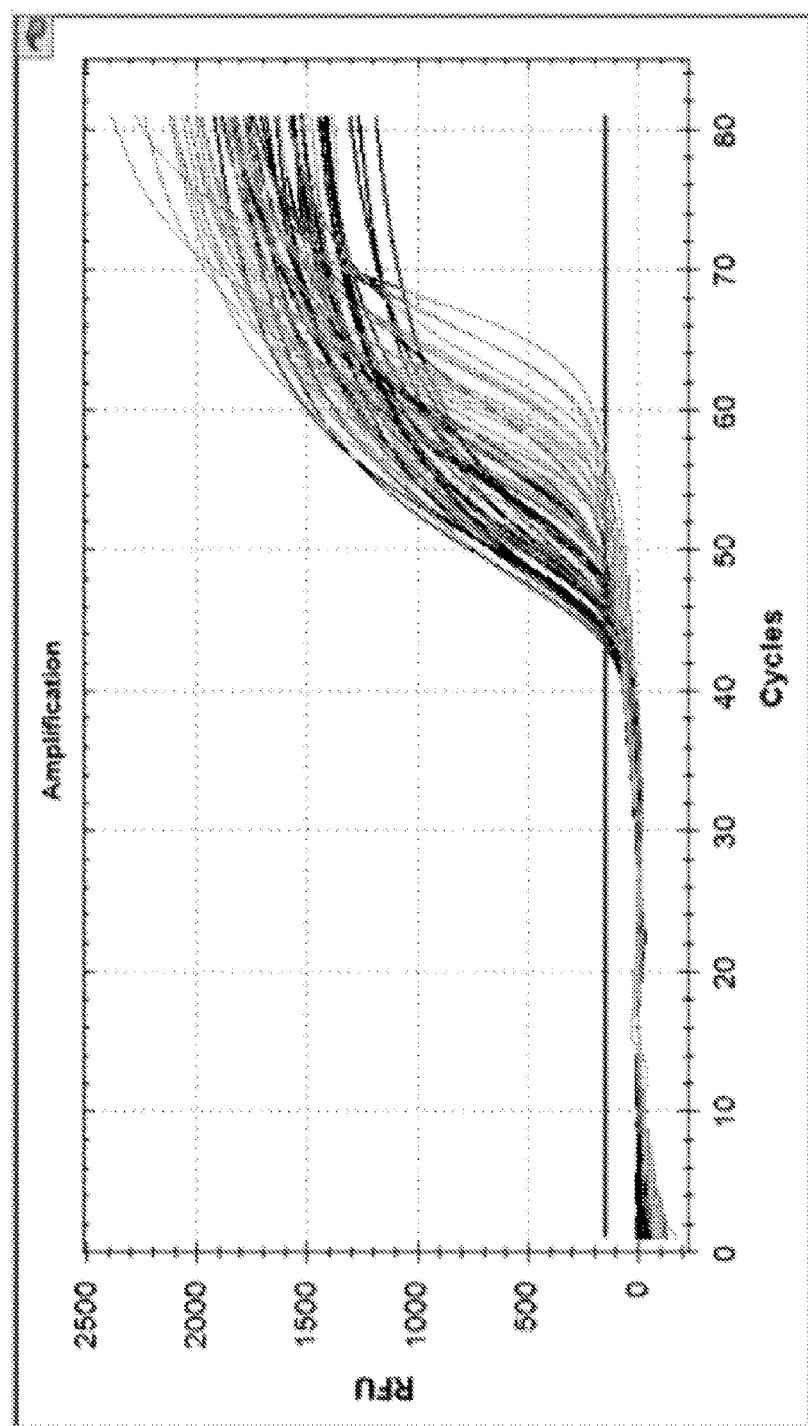


FIGURE 1A

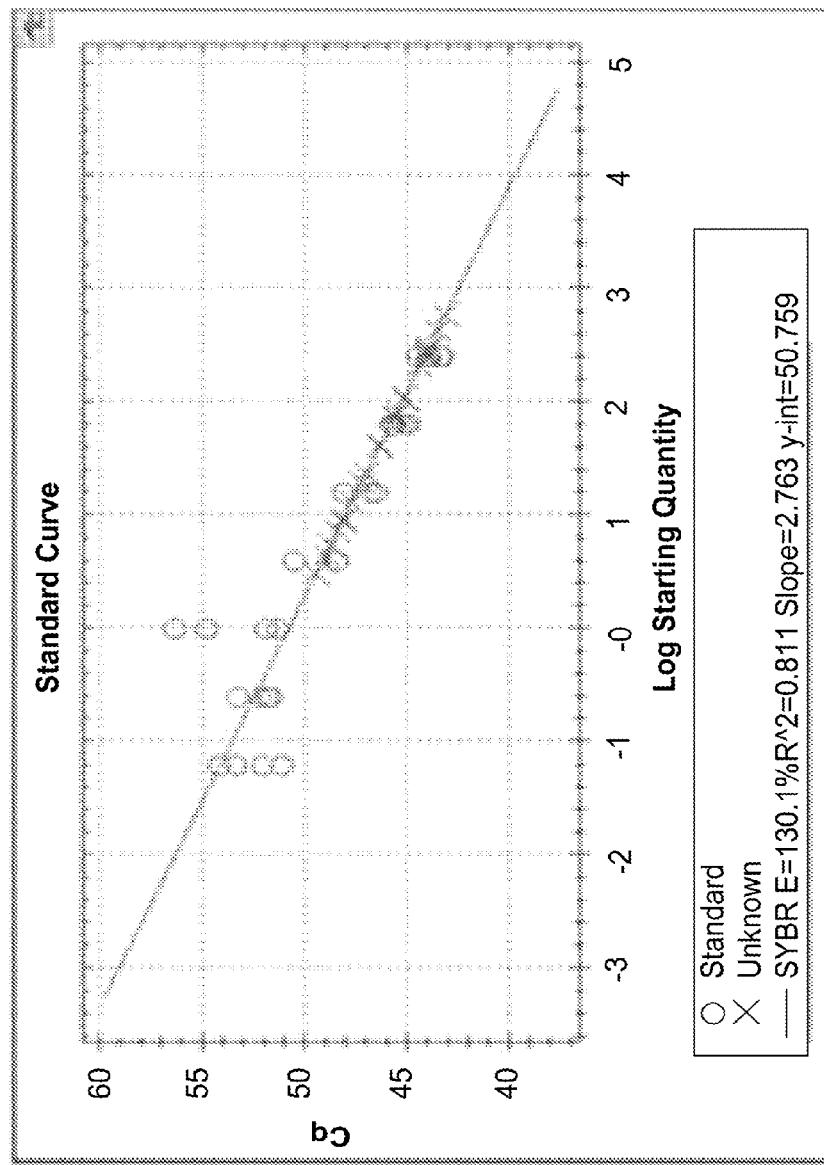


Fig. 1B

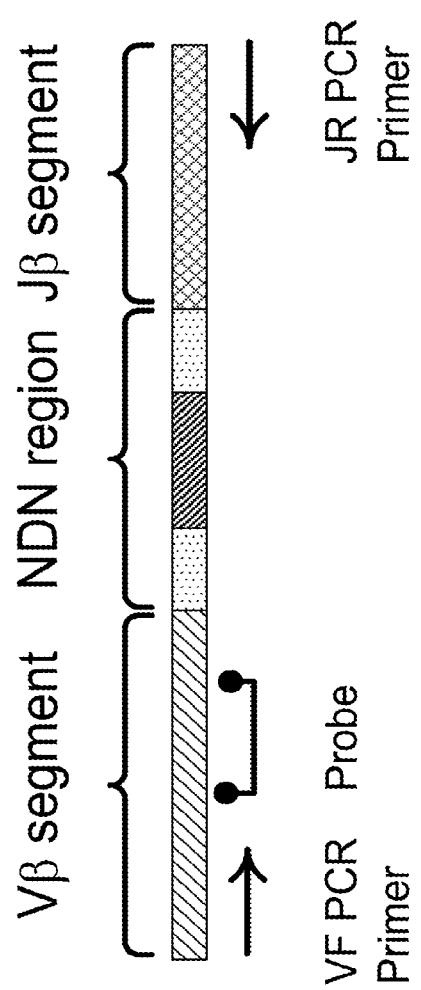


Fig. 2

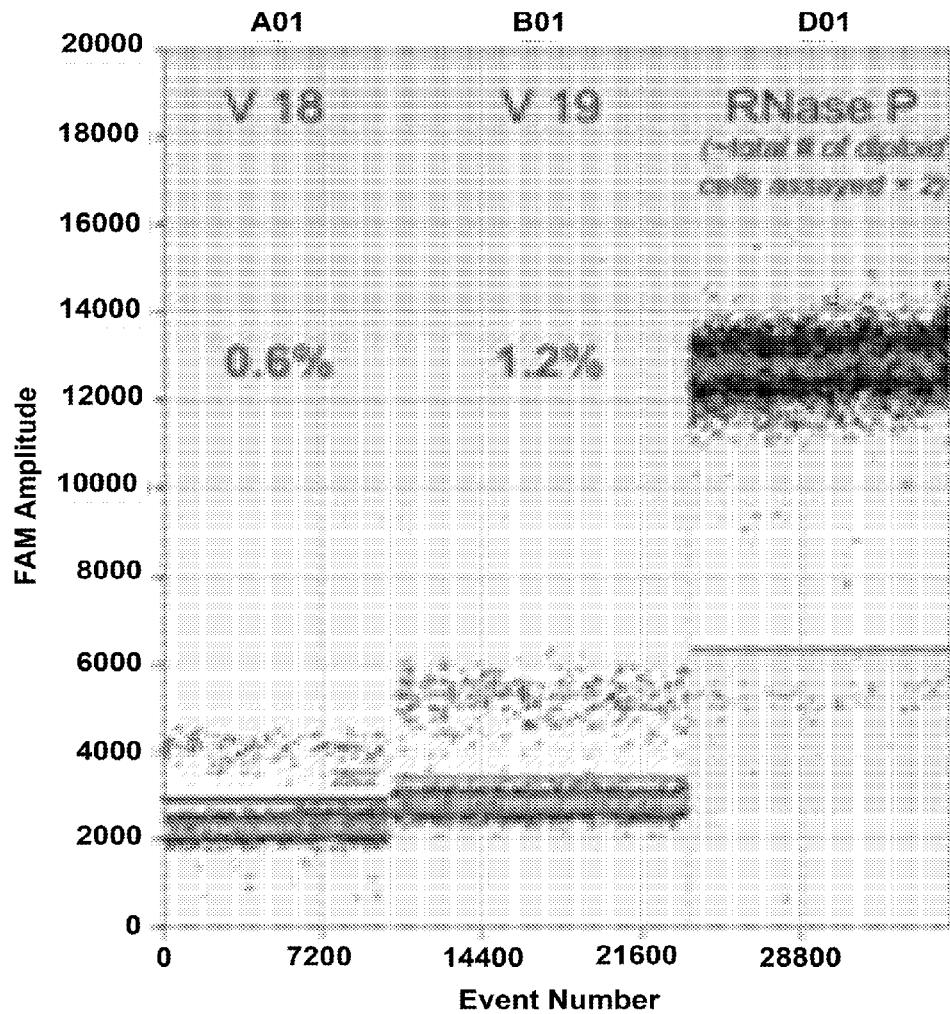


Fig. 3

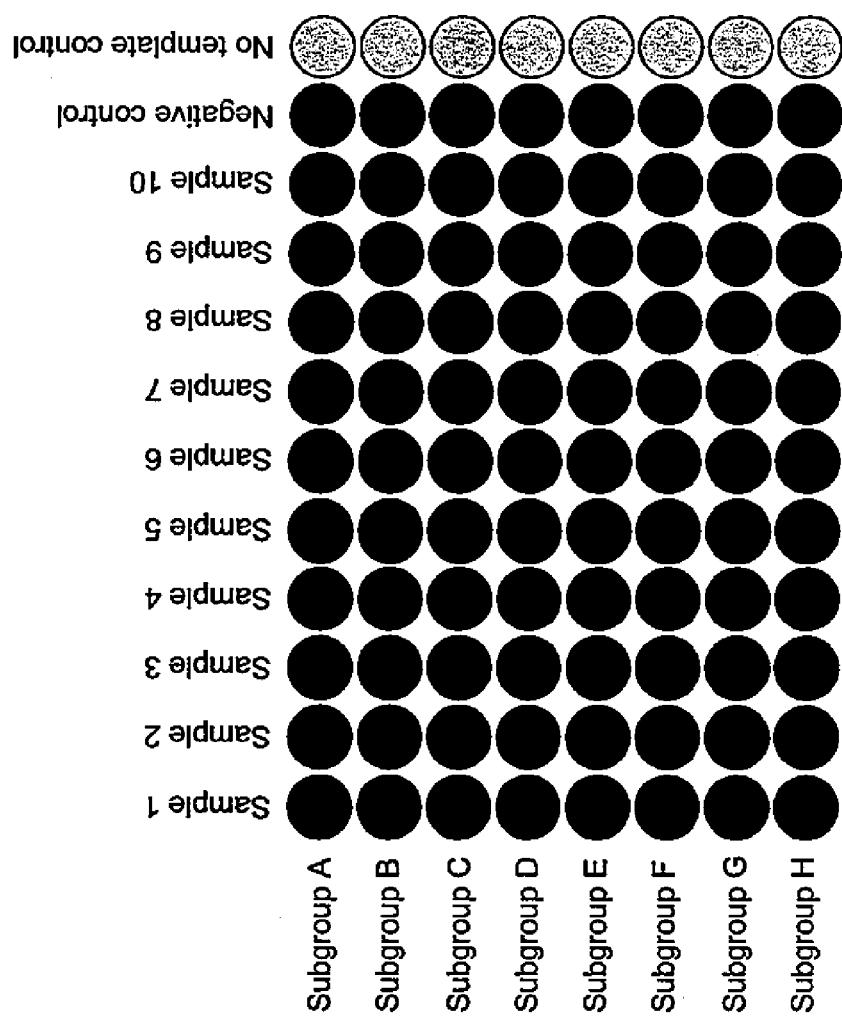


FIGURE 4

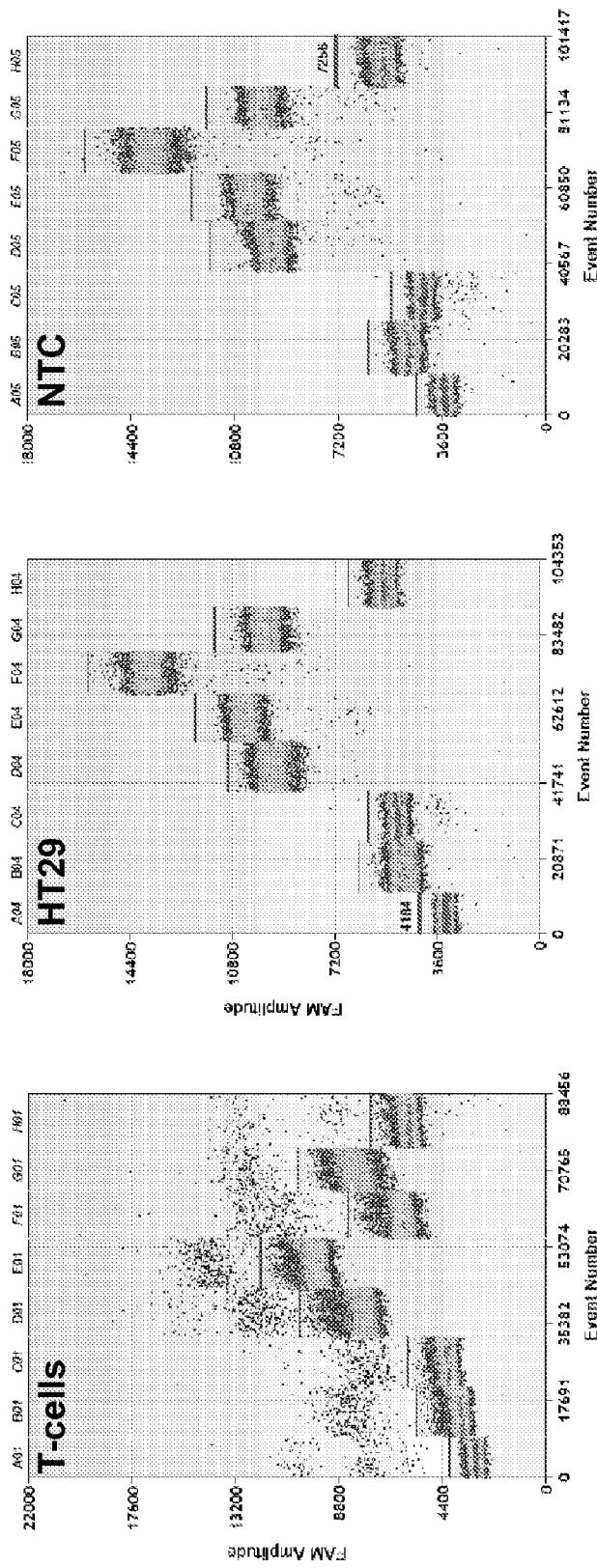


FIGURE 5A

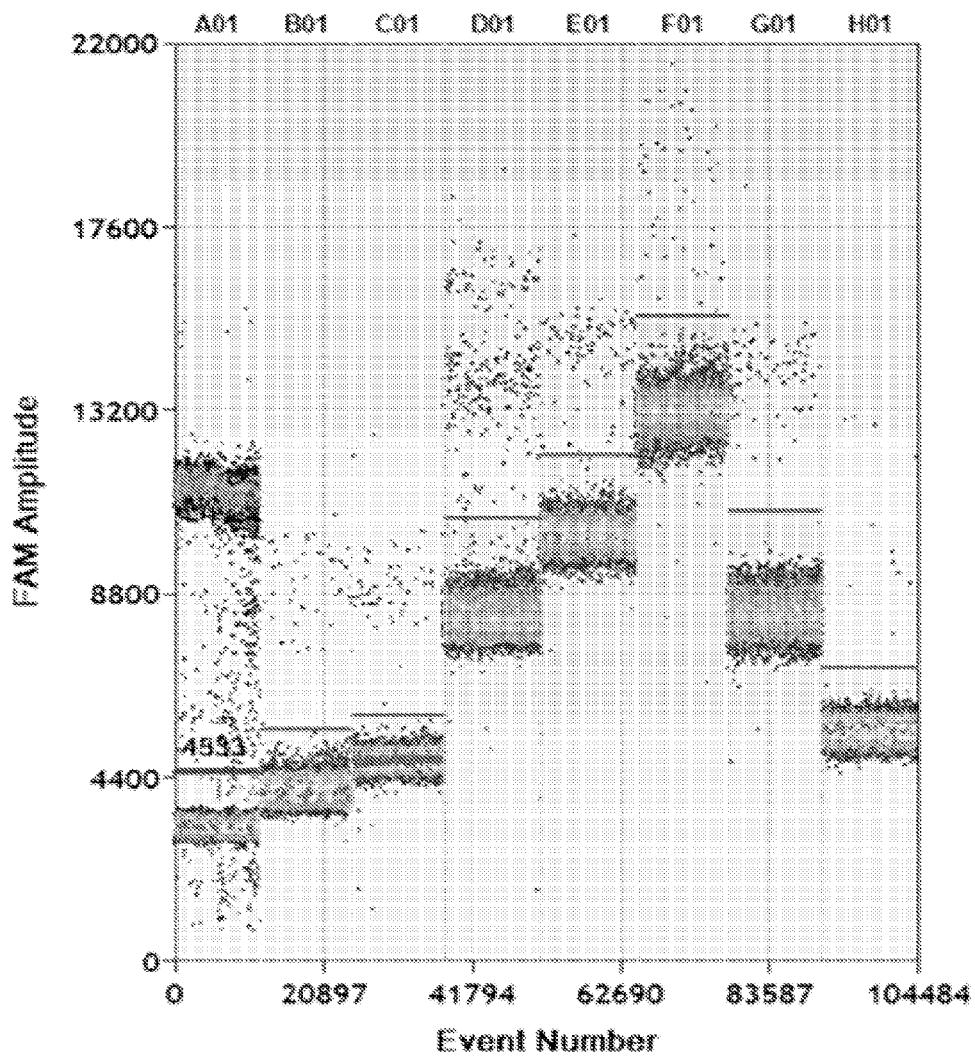


FIGURE 5B

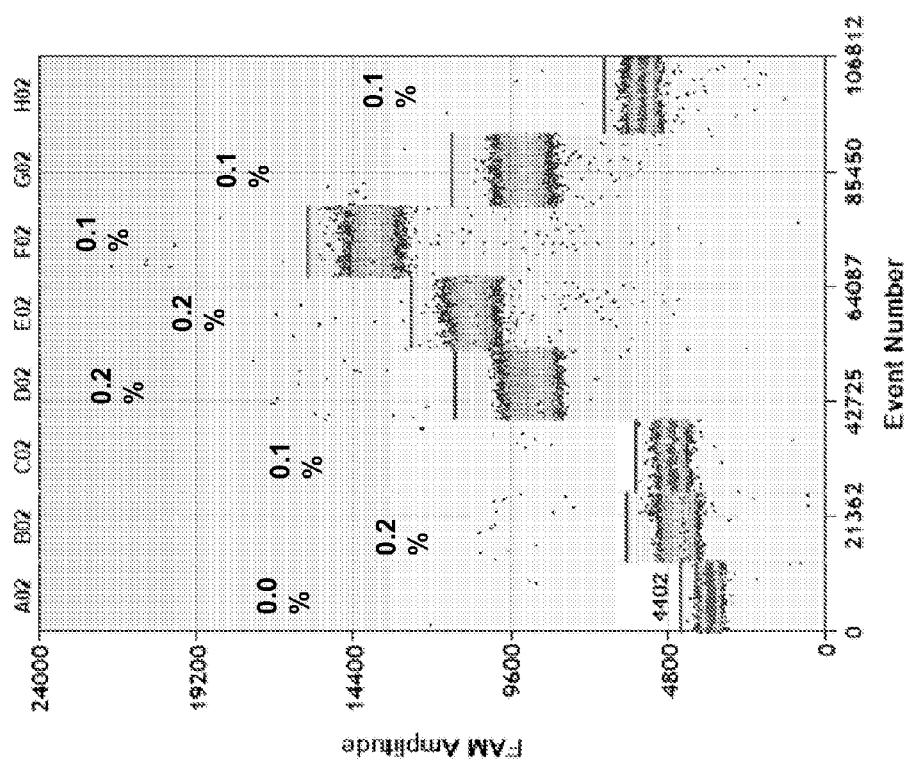


FIGURE 5C

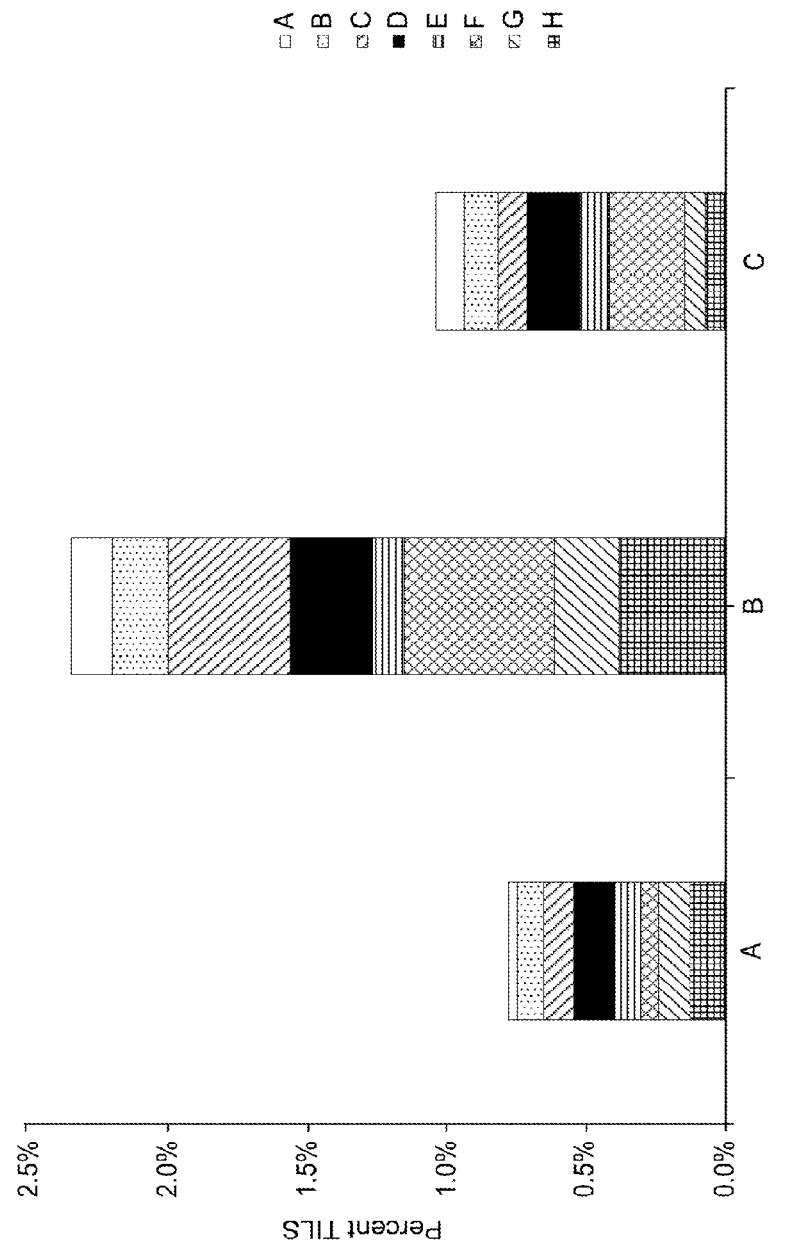


FIGURE 6

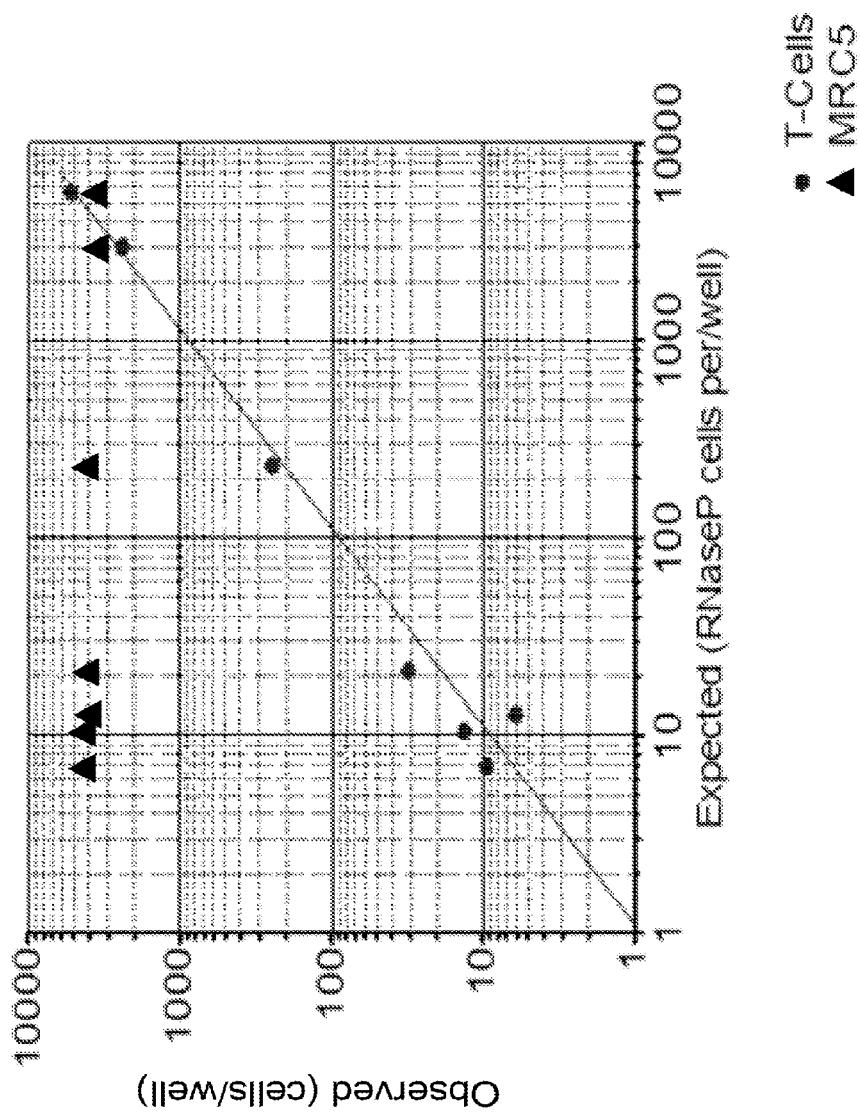


FIGURE 7

**QUANTIFICATION OF ADAPTIVE IMMUNE
CELL GENOMES IN A COMPLEX MIXTURE
OF CELLS**

**CROSS REFERENCE TO RELATED
APPLICATIONS**

This application is a continuation of U.S. patent application Ser. No. 14/199,167, filed Mar. 6, 2014, titled, "Quantification of Adaptive Immune Cell Genomes in a Complex Mixture of Cells", which is a continuation of U.S. patent application Ser. No. 13/656,265, filed Oct. 19, 2012, titled, "Quantification of Adaptive Immune Cell Genomes in a Complex Mixture of Cells", which claims the benefit of U.S. Provisional Patent Application Ser. No. 61/550,311, filed Oct. 21, 2011, titled, "Quantification of Adaptive Immune Cell Genomes in a Complex Mixture of Cells", all of which are incorporated herein by reference, in their entirety, for all purposes.

SEQUENCE LISTING

The Sequence Listing associated with this application is provided in text format in lieu of a paper copy, and is hereby incorporated by reference into the specification. The name of the text file containing the Sequence Listing is 22442US_CRF_sequencelisting.txt. This text file was created on Feb. 20, 2014, is about 359,060 bytes in size, and is being submitted electronically via EFS-Web.

BACKGROUND

1. Technical Field

The present disclosure relates generally to the highly sensitive quantification of the relative representation of adaptive immune cells in complex mixtures of cells using multiplex digital polymerase chain reaction (dPCR) or multiplex quantitative polymerase chain reaction (qPCR). In particular, the present disclosure relates to methods for quantitative determination of lymphocyte presence in complex tissues including solid tissues, such as quantification of tumor-infiltrating lymphocyte (TIL) genomes as a relative proportion of all cellular genomes that are represented in a tumor DNA sample, or quantification of the genomes of lymphocytes that have infiltrated somatic tissue in the pathogenesis of inflammation, allergy or autoimmune disease or in transplanted organs as a relative proportion of all cellular genomes that are represented in a tissue DNA sample.

2. Description of the Related Art

The adaptive immune system protects higher organisms against infections and other pathological events that may be attributable to foreign substances, using adaptive immune receptors, the antigen-specific recognition proteins that are expressed by hematopoietic cells of the lymphoid lineage and that are capable of distinguishing self from non-self molecules in the host. These lymphocytes may be found in the circulation and tissues of a host, and their recirculation between blood and the lymphatics has been described, including their extravasation via lymph node high endothelial venules, as well as at sites of infection, inflammation, tissue injury and other clinical insults. (See, e.g., Stein et al., 2005 *Immunol.* 116:1-12; DeNucci et al., 2009 *Crit. Rev. Immunol.* 29:87-109; Marelli-Berg et al., 2010 *Immunol.* 130:158; Ward et al., 2009 *Biochem. J.* 418:13; Gonzalez et al., 2011 *Ann. Rev. Immunol.* 29:215; Kehrl et al., 2009 *Curr. Top. Microbiol. Immunol.* 334:107; Steinmetz et al., 2009 *Front. Biosci. (Schol. Ed.)* 1:13.)

Accordingly, the dynamic nature of movement by lymphocytes throughout a host organism is reflected in changes in the qualitative (e.g., antigen-specificity of the clonally expressed adaptive immune receptor (immunoglobulin or T cell receptor), T cell versus B cell, T helper (T_h) cell versus T regulatory (T_{reg}) cell, effector T cell versus memory T cell, etc.) and quantitative distribution of lymphocytes among tissues, as a function of changes in host immune status.

For example, numerous studies have found an association 10 between (i) the presence of tumor infiltrating lymphocytes (TIL) in a variety of solid tumors and (ii) patient prognosis and overall survival rates. In some studies, tumor infiltrating T cells having a specific phenotype (e.g., CD8⁺ and CD4⁺ T cells or regulatory T cells) are positive or negative predictors 15 of survival (e.g., Jochems et al., 2011 *Experimental Biol. Med.* 236:567-579). In certain cases, however, TIL count alone is a predictor of long-term survival (e.g., Katz et al., 2009 *Ann. Surg. Oncol.* 16:2524-2530). Thus, quantitative determination of TIL counts has high prognostic value in a 20 variety of cancers including colorectal, hepatocellular, gall-bladder, pancreatic, esophageal, ovarian endometrial, cervical, bladder and urothelial cancers. While more is known about the association of tumor-infiltrating T cells, B cells are also known to infiltrate tumors and studies have shown an 25 association of tumor-infiltrating B cells with survival advantage (e.g., Ladányi, et al., *Cancer Immunol. Immunother.* 60(12):1729-38, Jul. 21, 2011 (epub ahead of print)).

The quantitative determination of the presence of adaptive 30 immune cells (e.g., T and B lymphocytes) in diseased tissues may therefore provide useful information for diagnostic, prognostic and other purposes, such as in cancer, infection, inflammation, tissue injury and other conditions.

The adaptive immune system employs several strategies to 35 generate a repertoire of T- and B-cell antigen receptors with sufficient diversity to recognize the universe of potential pathogens. B lymphocytes mature to express antibodies (immunoglobulins, Igs) that occur as heterodimers of a heavy (H) a light (L) chain polypeptide, while T lymphocytes express 40 heterodimeric T cell receptors (TCR). The ability of T cells to recognize the universe of antigens associated with various cancers or infectious organisms is conferred by its T cell antigen receptor (TCR), which is made up of both an α (alpha) chain and a β (beta) chain or a γ (gamma) and a δ (delta) chain. The proteins which make up these chains are encoded by 45 DNA, which employs a unique mechanism for generating the tremendous diversity of the TCR. This multi-subunit immune recognition receptor associates with the CD3 complex and binds to peptides presented by the major histocompatibility complex (MHC) class I and II proteins on the surface of antigen-presenting cells (APCs). Binding of TCR to the anti-genic peptide on the APC is the central event in T cell activation, which occurs at an immunological synapse at the point of contact between the T cell and the APC.

Each TCR peptide contains variable complementarity 50 determining regions (CDRs), as well as framework regions (FRs) and a constant region. The sequence diversity of $\alpha\beta$ T cells is largely determined by the amino acid sequence of the third complementarity-determining region (CDR3) loops of the α and β chain variable domains, which diversity is a result 55 of recombination between variable (V_β), diversity (D_β), and joining (J_β) gene segments in the β chain locus, and between analogous V_α and J_α gene segments in the α chain locus, respectively. The existence of multiple such gene segments in the TCR α and β chain loci allows for a large number of 60 distinct CDR3 sequences to be encoded. CDR3 sequence diversity is further increased by independent addition and deletion of nucleotides at the V_β - D_β , D_β - J_β , and V_α - J_α junc-

tions during the process of TCR gene rearrangement. In this respect, immunocompetence is reflected in the diversity of TCRs.

The $\gamma\delta$ TCR is distinctive from the $\alpha\beta$ TCR in that it encodes a receptor that interacts closely with the innate immune system. TCR $\gamma\delta$, is expressed early in development, has specialized anatomical distribution, has unique pathogen and small-molecule specificities, and has a broad spectrum of innate and adaptive cellular interactions. A biased pattern of TCR γ V and J segment expression is established early in ontogeny as the restricted subsets of TCR $\gamma\delta$ cells populate the mouth, skin, gut, vagina, and lungs prenatally. Consequently, the diverse TCR γ repertoire in adult tissues is the result of extensive peripheral expansion following stimulation by environmental exposure to pathogens and toxic molecules.

Igs expressed by B cells are proteins consisting of four polypeptide chains, two heavy chains (H chains) and two light chains (L chains), forming an H₂L₂ structure. Each pair of H and L chains contains a hypervariable domain, consisting of a V_L and a V_H region, and a constant domain. The H chains of Igs are of several types, μ , δ , γ , α , and β . The diversity of Igs within an individual is mainly determined by the hypervariable domain. Similar to the TCR, the V domain of H chains is created by the combinatorial joining of the V_H, D_H, and J_H gene segments. Hypervariable domain sequence diversity is further increased by independent addition and deletion of nucleotides at the V_H-D_H, D_H-J_H, and V_H-J_H junctions during the process of Ig gene rearrangement. In this respect, immunocompetence is reflected in the diversity of Igs.

Quantitative characterization of adaptive immune cells based on the presence in such cells of functionally rearranged Ig and TCR encoding genes that direct productive expression of adaptive immune receptors has been achieved using biological samples from which adaptive immune cells can be readily isolated in significant numbers, such as blood, lymph or other biological fluids. In these samples, adaptive immune cells occur as particles in fluid suspension. See, e.g., US 2010/0330571; see also, e.g., Murphy, *Janeway's Immunobiology* (8th Ed.), 2011 Garland Science, NY, Appendix I, pp. 717-762.

Current approaches to the detection and quantification of adaptive immune cells in tissues or organs from which adaptive immune cells cannot be readily isolated, however, are far more limited. For example, in solid tissues and solid tumors, adaptive immune cell detection typically requires histological detection in a small, non-representative sample such as a fixed or frozen section of a biopsy specimen, using laborious and at most semi-quantitative techniques such as immunohistochemistry or in situ hybridization (e.g., Bancroft and Gamble, *Theory and Practice of Histological Techniques*, Churchill Livingstone, 2007; Carson and Hladik, *Histotechnology: A Self-Instructional Text*, 2009 Am. Soc. Clin. Pathol.). In conventional practice, the excised tissue may be cut into a plurality of serial histological sections along substantially parallel planes, for analysis by any of a number of known histological, histochemical, immunohistological, histopathologic, microscopic (including morphometric analysis and/or three-dimensional reconstruction), cytological, biochemical, pharmacological, molecular biological, immunochemical, imaging or other analytical techniques, which techniques are known to persons skilled in the relevant art. See, e.g., Bancroft and Gamble, *Theory and Practice of Histological Techniques* (6th Ed.), 2007 Churchill Livingstone, Oxford, UK; Kiernan, *Histological and Histochemical Methods: Theory and Practice*, 2001 Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y.; M. A. Hayat (Ed.), *Cancer Imaging*—Vols. 1 and 2, 2007 Academic Press, NY.

Efforts to obtain meaningful quantitative data from such approaches are severely limited with regard to the number of adaptive immune cells that may have infiltrated a tissue, for instance, where high statistical significance cannot be achieved when sample collection depends on the number of events that can be detected by observation of a finite number of small fields on microscope slides. Alternatively, a tissue sample must be mechanically and/or enzymatically dissociated to produce a single-cell suspension that is amenable to flow immunocyt fluorimetric analysis (e.g., Murphy, 2011, pp. 740-742), although such time-consuming and labor-intensive steps are likely to result in incomplete recovery of lymphocytes from the sample due to loss or destruction of a portion of the sample in the course of handling. These and related limitations of the current approaches compromise the quality of quantitative data that may be obtained.

Clearly there is a need for an improved method for quantifying adaptive immune cells in a complex biological sample containing a mixture of cells that are not all adaptive immune cells, without requiring the isolation of adaptive immune cells from the sample, e.g., without having to separate the adaptive immune cells from the non-adaptive immune cells. The presently described embodiments address this need and offer other related advantages.

BRIEF SUMMARY

In one aspect the present invention provides a method for quantifying the relative representation of adaptive immune cells in a test biological sample that comprises a mixture of cells, the mixture comprising adaptive immune cells and cells that are not adaptive immune cells, the method comprising (a) distributing test sample template DNA extracted from the test biological sample to form a set of assay samples, (b) amplifying said test sample template DNA in the set of assay samples in a multiplex digital polymerase chain reaction (dPCR) that comprises: (1) (i) a plurality of V-segment oligonucleotide primers that are each independently capable of specifically hybridizing to at least one polynucleotide encoding a T cell receptor (TCR) V-region polypeptide or an immunoglobulin (Ig) V-region polypeptide, wherein each V-segment primer comprises a nucleotide sequence of at least 15 contiguous nucleotides that is complementary to at least one functional TCR or Ig V-encoding gene segment and wherein the plurality of V-segment primers specifically hybridize to substantially all functional TCR or Ig V-encoding gene segments that are present in the test sample, and (ii) a plurality of J-segment oligonucleotide primers that are each independently capable of specifically hybridizing to at least one polynucleotide encoding a T cell receptor (TCR) J-region polypeptide or an immunoglobulin (Ig) J-region polypeptide, wherein each J-segment primer comprises a nucleotide sequence of at least 15 contiguous nucleotides that is complementary to at least one functional TCR or Ig J-encoding gene segment and wherein the plurality of J-segment primers specifically hybridize to substantially all functional TCR or Ig J-encoding gene segments that are present in the test sample, wherein the V-segment and J-segment primers are capable of amplifying in said multiplex dPCR substantially all rearranged TCR or Ig CDR3-encoding regions in the test sample to produce a multiplicity of amplified rearranged DNA molecules from the adaptive immune cells in the test sample; and (2) a set of control primers to produce an internal control gene amplification product, wherein the set of control primers amplifies an internal control gene segment that is not specific to adaptive immune cells; and (c) comparing a first number of assay samples that detectably contain said multiplicity of

amplified rearranged DNA molecules of (b)(1) with a second number of assay samples that detectably contain said internal control gene amplification product of (b)(2), and therefrom quantifying the relative representation of adaptive immune cells in said test biological sample.

In certain embodiments the plurality of V-segment oligonucleotide primers and the plurality of J-segment oligonucleotide primers comprise the sequences set forth in SEQ ID NOS:1-65, 644-708 and 843-883. In certain embodiments either or both of (i) the V-segment oligonucleotide primers comprise one or a plurality of oligonucleotides that exhibit at least 90% sequence identity to one or more of the nucleotide sequences set forth in SEQ ID NOS:1-52, 644-685, and 880-883, and (ii) the J-segment primers comprise one or a plurality of oligonucleotides that exhibit at least 90% sequence identity to one or more of the nucleotide sequences set forth in SEQ ID NOS:53-65, 696-708, and 880-883. In certain embodiments each amplified rearranged DNA molecule in the multiplicity of amplified rearranged DNA molecules is less than 600 nucleotides in length. In certain embodiments each functional TCR or Ig V-encoding gene segment comprises a V gene recombination signal sequence (RSS) and each functional TCR or Ig J-encoding gene segment comprises a J gene RSS, and wherein each amplified rearranged DNA molecule comprises (i) at least 10, 20, 30 or 40 contiguous nucleotides of a sense strand of the TCR or Ig V-encoding gene segment, said at least 10, 20, 30 or 40 contiguous nucleotides being situated 5' to the V gene RSS and (ii) at least 10, 20 or 30 contiguous nucleotides of a sense strand of the TCR or Ig J-encoding gene segment, said at least 10, 20 or 30 contiguous nucleotides being situated 3' to the J gene RSS.

In certain embodiments the above described method is capable of detecting a presence of at least ten adaptive immune cells per 10,000 cells in the mixture of cells. In certain embodiments the adaptive immune cells are T cells and in certain other embodiments the adaptive immune cells are B cells. In certain embodiments the biological sample is fresh tissue, frozen tissue, or fixed tissue. In certain embodiments the rearranged TCR or Ig CDR3-encoding regions are selected from rearranged TCR α CDR3-encoding regions, TCR β CDR3-encoding regions, TCR γ CDR3-encoding regions, TCR δ CDR3-encoding regions, IgH CDR3-encoding regions, IgK CDR3-encoding regions, and Ig λ CDR3-encoding regions. In certain embodiments the test biological sample comprises human cells, mouse cells, or rat cells. In certain embodiments either or both of the first and second numbers of assay samples are determined by detecting fluorescence of a non-specific DNA-intercalating dye in the assay samples. In certain embodiments the first number of assay samples is determined by detecting fluorescence of a labeled probe or of multiple labeled probes that specifically hybridize to the multiplicity of amplified rearranged DNA molecules, and the second number of assay samples is determined by detecting fluorescence of a labeled probe that specifically hybridizes to the internal control gene amplification products. In certain further embodiments the labeled probe that specifically hybridizes to the multiplicity of amplified rearranged DNA molecules comprises a sequence selected from SEQ ID NOS:66 and 709-839, or one or more of the multiple labeled probes that specifically hybridize to the multiplicity of amplified rearranged DNA molecules comprise one or more sequence selected from SEQ ID NOS:66 and 709-839.

In certain embodiments the test biological sample comprises somatic tissue, which in certain further embodiments is from a subject having an autoimmune disease and the tissue is targeted by an autoimmune reaction. In certain still further embodiments the autoimmune disease is selected from type 1

diabetes, rheumatoid arthritis, multiple sclerosis, Crohn's disease, Graves' disease, Addison's disease, celiac disease, Sjögren's, psoriasis, Guillain-Barre syndrome, and myasthenia gravis. In certain embodiments the somatic tissue comprises neoplastic tissue, which in certain further embodiments is obtained or derived from a solid tumor. In certain embodiments the somatic tissue is from a transplanted organ, which in certain further embodiments is selected from liver, lung, kidney, heart, spleen, pancreas, skin, intestine, and thymus. In certain further embodiments of the above described methods, the plurality of V-segment oligonucleotide primers and the plurality of J-segment oligonucleotide primers are RN2 modified.

Turning to another aspect of the present invention there is provided a method for assessing an effect of a therapeutic treatment on relative representation of adaptive immune cells in at least one tissue of a subject, the tissue comprising adaptive immune cells and cells that are not adaptive immune cells, the method comprising (I) obtaining one or a plurality of test biological samples from a first tissue of the subject at one or a plurality of time points prior to administering the therapeutic treatment, wherein the test biological sample contains DNA from a mixture of cells, the mixture comprising adaptive immune cells and cells that are not adaptive immune cells; (II) obtaining one or a plurality of test biological samples from a second tissue of the subject at one or a plurality of time points after administering the therapeutic treatment, wherein the test biological sample contains DNA from a mixture of cells, the mixture comprising adaptive immune cells and cells that are not adaptive immune cells; (III) for each of said test biological samples from (I) and (II): (a) distributing test sample template DNA extracted from the test biological sample to form a set of assay samples, (b) amplifying said test sample template DNA in the set of assay samples in a multiplex digital polymerase chain reaction (dPCR) that comprises: (1) (i) a plurality of V-segment oligonucleotide primers that are each independently capable of specifically hybridizing to at least one polynucleotide encoding a T cell receptor (TCR) V-region polypeptide or an immunoglobulin (Ig) V-region polypeptide, wherein each V-segment primer comprises a nucleotide sequence of at least 15 contiguous nucleotides that is complementary to at least one functional TCR or Ig V-encoding gene segment and wherein the plurality of V-segment primers specifically hybridize to substantially all functional TCR or Ig V-encoding gene segments that are present in the test sample, and (ii) a plurality of J-segment oligonucleotide primers that are each independently capable of specifically hybridizing to at least one polynucleotide encoding a T cell receptor (TCR) J-region polypeptide or an immunoglobulin (Ig) J-region polypeptide, wherein each J-segment primer comprises a nucleotide sequence of at least 15 contiguous nucleotides that is complementary to at least one functional TCR or Ig J-encoding gene segment and wherein the plurality of J-segment primers specifically hybridize to substantially all functional TCR or Ig J-encoding gene segments that are present in the test sample, wherein the V-segment and J-segment primers are capable of amplifying in said multiplex dPCR of substantially all rearranged TCR or Ig CDR3-encoding regions in the test sample to produce a multiplicity of amplified rearranged DNA molecules from the adaptive immune cells in the test sample; and (2) a set of control primers to produce an internal control gene amplification product, wherein the set of control primers amplifies an internal control gene DNA segment that is not specific to adaptive immune cells; and (c) comparing a first number of assay samples that detectably contain said multiplicity of amplified rearranged DNA molecules of (b)(1) with

a second number of assay samples that detectably contain said internal control gene amplification product of (b)(2), and therefrom quantifying the relative representation of adaptive immune cells in said test biological sample; and (IV) comparing the relative representation of adaptive immune cells in at least one test biological sample obtained at a time point prior to administering the therapeutic treatment to the relative representation of adaptive immune cells in at least one test biological sample obtained at a time point after administering the therapeutic treatment, and thereby assessing an effect of the therapeutic treatment on relative representation of adaptive immune cells in at least one tissue of a subject.

In certain further embodiments the first and second tissues are the same tissue, and in certain other further embodiments the first and second tissues are different tissues. In certain embodiments the method assesses a dose-related effect of the therapeutic treatment, wherein a plurality of test biological samples are obtained from the second tissue of the subject at a plurality of time points after administering the therapeutic treatment, and wherein the therapeutic treatment is administered at a plurality of different dosages. In certain embodiments the method assesses a prognosis for the subject receiving the therapeutic treatment, wherein an altered relative representation of adaptive immune cells in at least one test biological sample obtained at a time point after administering the therapeutic treatment, compared to the relative representation of adaptive immune cells in at least one test biological sample obtained at a time point prior to administering the therapeutic treatment, indicates an effect of the therapeutic treatment on relative representation of adaptive immune cells in at least one tissue of a subject. In certain embodiments the method is selected from: (i) the method in which the subject has cancer and an increased relative representation of adaptive immune cells in at least one test biological sample obtained at a time point after administering the therapeutic treatment compared to the relative representation of adaptive immune cells in at least one test biological sample obtained at a time point prior to administering the therapeutic treatment, indicates a beneficial effect of the therapeutic treatment; (ii) the method in which the subject has an autoimmune disease and a decreased relative representation of adaptive immune cells in at least one test biological sample obtained at a time point after administering the therapeutic treatment compared to the relative representation of adaptive immune cells in at least one test biological sample obtained at a time point prior to administering the therapeutic treatment, indicates a beneficial effect of the therapeutic treatment; and (iii) the method in which the subject has a transplanted organ and a decreased relative representation of adaptive immune cells in at least one test biological sample from the transplanted organ obtained at a time point after administering the therapeutic treatment compared to the relative representation of adaptive immune cells in at least one test biological sample from the transplanted organ obtained at a time point prior to administering the therapeutic treatment, indicates a beneficial effect of the therapeutic treatment.

In certain embodiments of the above described methods, the method further comprises determining a polynucleotide sequence for each amplified rearranged DNA molecule from the population of adaptive immune cells in the test sample. In certain embodiments the plurality of V-segment oligonucleotide primers and the plurality of J-segment oligonucleotide primers comprise at least one of (1) the sequences set forth in SEQ ID NOS:1-65, (2) the sequences set forth in SEQ ID NOS:66-214, (3) the sequences set forth in SEQ ID NOS:215-238, (4) the sequences set forth in SEQ ID NOS:239-545, (5) the sequences set forth in SEQ ID NOS:546-549 and

634-637, (6) the sequences set forth in SEQ ID NOS:550-633 and 638-643, (7) the sequences set forth in SEQ ID NOS:644-708, (8) the sequences set forth in SEQ ID NOS:644-773, (9) the sequences set forth in SEQ ID NOS:843-879, (10) the sequences set forth in SEQ ID NOS:880-883, and (11) portions of sequences (1) to (10) that are at least 15 nucleotides in length. In certain embodiments either or both of: (i) the V-segment oligonucleotide primers comprise one or a plurality of oligonucleotides that exhibit at least 90% sequence identity to one or more of: (1) the nucleotide sequences set forth in SEQ ID NOS:1-52, (2) the nucleotide sequences set forth in SEQ ID NOS:67-201, (3) the nucleotide sequences set forth in SEQ ID NOS:221-238, (4) the nucleotide sequences set forth in SEQ ID NOS:255-545, (5) the nucleotide sequences set forth in SEQ ID NOS:546-549, (6) the nucleotide sequences set forth in SEQ ID NOS:550-633, (7) the nucleotide sequences set forth in SEQ ID NOS:644-695, (8) the nucleotide sequences set forth in SEQ ID NOS:843-879, and (9) portions of sequences (1) to (8) that are at least 15 nucleotides in length; and (ii) the J-segment primers comprise one or a plurality of oligonucleotides that exhibit at least 90% sequence identity to one or more of: (1) the nucleotide sequences set forth in SEQ ID NOS:53-65, (2) the nucleotide sequences set forth in SEQ ID NOS:202-214, (3) the nucleotide sequences set forth in SEQ ID NOS:215-220, (4) the nucleotide sequences set forth in SEQ ID NOS:239-254, (5) the nucleotide sequences set forth in SEQ ID NOS:634-637, (6) the nucleotide sequences set forth in SEQ ID NOS:638-643, (7) the nucleotide sequences set forth in SEQ ID NOS:696-708, (8) the nucleotide sequences set forth in SEQ ID NOS:880-883, and (9) portions of sequences (1) to (8) that are at least 15 nucleotides in length.

Turning to another embodiment of the presently disclosed invention, there is provided a method for quantifying the relative representation of adaptive immune cell DNA in a test biological sample that contains DNA from a mixture of cells, the mixture comprising adaptive immune cells and cells that are not adaptive immune cells, the method comprising: (a) amplifying test sample template DNA extracted from the test biological sample in a multiplex quantitative polymerase chain reaction (qPCR) that comprises: (i) a plurality of V-segment oligonucleotide primers that are each independently capable of specifically hybridizing to at least one polynucleotide encoding a T cell receptor (TCR) V-region polypeptide or an immunoglobulin (Ig) V-region polypeptide, wherein each V-segment primer comprises a nucleotide sequence of at least 15 contiguous nucleotides that is complementary to at least one functional TCR or Ig V-encoding gene segment and wherein the plurality of V-segment primers specifically hybridize to substantially all functional TCR or Ig V-encoding gene segments that are present in the test sample, and (ii) a plurality of J-segment oligonucleotide primers that are each independently capable of specifically hybridizing to at least one polynucleotide encoding a T cell receptor (TCR) J-region polypeptide or an immunoglobulin (Ig) J-region polypeptide, wherein each J-segment primer comprises a nucleotide sequence of at least 15 contiguous nucleotides that is complementary to at least one functional TCR or Ig J-encoding gene segment and wherein the plurality of J-segment primers specifically hybridize to substantially all functional TCR or Ig J-encoding gene segments that are present in the test sample, wherein the V-segment and J-segment primers are capable of promoting amplification in said multiplex polymerase chain reaction (PCR) of substantially all rearranged TCR or Ig CDR3-encoding regions in the test sample to produce a multiplicity of amplified rearranged DNA molecules from a population of adaptive immune cells in the test sample; and

(b) concurrently with said step of amplifying, measuring at one or a plurality of time points a first DNA signal level that is detectable in said multiplicity of amplified rearranged DNA molecules of (a); (c) comparing at said one or plurality of time points the first DNA signal level measured in (b) to a second DNA signal level that is detectable in amplification products of a known amount of control adaptive immune cell template DNA extracted from a control adaptive immune cell sample that has been amplified by the plurality of V-segment oligonucleotide primers and the plurality of J-segment oligonucleotide primers, and therefrom quantifying a relative amount of adaptive immune cell DNA in the test sample template DNA extracted from the test biological sample; and (d) determining, from the relative amount of adaptive immune cell DNA quantified in (c), the relative representation of adaptive immune cell DNA in the test biological sample.

In certain embodiments the plurality of V-segment oligonucleotide primers and the plurality of J-segment oligonucleotide primers comprise the sequences set forth in SEQ ID NOS:1-65, 644-708, and 843-883. In certain embodiments either or both of: (i) the V-segment oligonucleotide primers comprise one or a plurality of oligonucleotides that exhibit at least 90% sequence identity to one or more of the nucleotide sequences set forth in SEQ ID NOS:1-52, 644-695, and 843-879; and (ii) the J-segment primers comprise one or a plurality of oligonucleotides that exhibit at least 90% sequence identity to one or more of the nucleotide sequences set forth in SEQ ID NOS:53-65, 696-708, and 880-883. In certain embodiments each amplified rearranged DNA molecule in the multiplicity of amplified rearranged DNA molecules is less than 600 nucleotides in length. In certain embodiments each functional TCR or Ig V-encoding gene segment comprises a V gene recombination signal sequence (RSS) and each functional TCR or Ig J-encoding gene segment comprises a J gene RSS, and wherein each amplified rearranged DNA molecule comprises (i) at least 10, 20, 30 or 40 contiguous nucleotides of a sense strand of the TCR or Ig V-encoding gene segment, said at least 10, 20, 30 or 40 contiguous nucleotides being situated 5' to the V gene RSS and (ii) at least 10, 20 or 30 contiguous nucleotides of a sense strand of the TCR or Ig J-encoding gene segment, said at least 10, 20 or 30 contiguous nucleotides being situated 3' to the J gene RSS. In certain embodiments the above described method is capable of detecting a presence of at least ten adaptive immune cells per 10,000 cells in the mixture of cells. In certain embodiments the adaptive immune cells are T cells. In certain embodiments the adaptive immune cells are B cells. In certain embodiments the biological sample is fresh tissue, frozen tissue, or fixed tissue. In certain embodiments the rearranged TCR or Ig CDR3-encoding regions are selected from rearranged TCR α CDR3-encoding regions, TCR β CDR3-encoding regions, TCR γ CDR3-encoding regions, TCR δ , CDR3-encoding regions, IgH CDR3-encoding regions, Igk CDR3-encoding regions, and Ig λ CDR3-encoding regions.

In certain further embodiments of the above described methods, the test biological sample and the control adaptive immune cell sample comprise cells that are selected from human cells, mouse cells and rat cells. In certain embodiments either or both of the first and second DNA signal levels are measured by detecting fluorescence of a non-specific DNA-intercalating dye. In certain embodiments the first DNA signal level is measured by detecting fluorescence of a labeled probe or of multiple labeled probes that specifically hybridize to the multiplicity of amplified rearranged DNA molecules and the second DNA signal level is measured by detecting fluorescence of a labeled probe or of multiple labeled probes that specifically hybridize to the amplification

products of the control adaptive immune cell template DNA. In certain further embodiments the labeled probe that specifically hybridizes to the multiplicity of amplified rearranged DNA molecules comprises a sequence selected from SEQ ID NOS:66 and 709-839, or one or more of the multiple labeled probes that specifically hybridize to the multiplicity of amplified rearranged DNA molecules comprise a sequence selected from SEQ ID NOS:66 and 709-839.

In certain further embodiments of the above described methods, the method comprises quantifying a relative amount of DNA in the mixture of cells that comprises adaptive immune cells and cells that are not adaptive immune cells, the method comprising: (e) amplifying test sample template DNA extracted from the test biological sample with a set of control primers to produce internal control gene amplification products, wherein the set of control primers amplifies an internal control gene DNA segment that is not specific to adaptive immune cells; (f) concurrently with step (e), measuring at one or a plurality of time points a third DNA signal level that is detectable in the amplification products of (e); (g) comparing, at said one or plurality of time points, the third DNA signal level in (f) to a fourth DNA signal level that is detectable in amplification products of a known amount of internal control gene DNA that has been amplified by the control primers, and therefrom quantifying a relative amount of internal control gene DNA in the test sample template DNA extracted from the test biological sample; and (h) determining, from the relative amount of internal control gene DNA quantified in (g), the relative amount of DNA in the mixture of cells.

In certain further embodiments the control primers are present in the qPCR reaction of (a). In certain embodiments, in step (e) the control primers are present in a qPCR reaction that is separate from the qPCR reaction of (a). In certain embodiments the test biological sample comprises somatic tissue, which in certain further embodiments is from a subject having an autoimmune disease and the tissue is targeted by an autoimmune reaction. In certain still further embodiments the autoimmune disease is selected from type 1 diabetes, rheumatoid arthritis, multiple sclerosis, Crohn's disease, Graves' disease, Addison's disease, celiac disease, Sjögren's, psoriasis, Guillain-Barre syndrome, and myasthenia gravis. In certain embodiments the somatic tissue comprises neoplastic tissue, which in certain further embodiments is obtained or derived from a solid tumor. In certain other embodiments the somatic tissue is from a transplanted organ, which in certain further embodiments is selected from liver, lung, kidney, heart, spleen, pancreas, skin, intestine, and thymus. In certain embodiments the plurality of V-segment oligonucleotide primers and the plurality of J-segment oligonucleotide primers are RN2 modified.

Turning to another embodiment, there is provided herein a method for assessing an effect of a therapeutic treatment on relative representation of adaptive immune cells in at least one tissue of a subject, the tissue comprising adaptive immune cells and cells that are not adaptive immune cells, the method comprising: (I) obtaining one or a plurality of test biological samples from a first tissue of the subject at one or a plurality of time points prior to administering the therapeutic treatment, wherein the test biological sample contains DNA from a mixture of cells, the mixture comprising adaptive immune cells and cells that are not adaptive immune cells; (II) obtaining one or a plurality of test biological samples from a second tissue of the subject at one or a plurality of time points after administering the therapeutic treatment, wherein the test biological sample contains DNA from a mixture of cells, the mixture comprising adaptive immune

11

cells and cells that are not adaptive immune cells; (III) for each of said test biological samples from (I) and (II): (a) amplifying test sample template DNA extracted from the test biological sample in a multiplex quantitative polymerase chain reaction (qPCR) that comprises: (i) a plurality of V-segment oligonucleotide primers that are each independently capable of specifically hybridizing to at least one polynucleotide encoding a T cell receptor (TCR) V-region polypeptide or an immunoglobulin (Ig) V-region polypeptide, wherein each V-segment primer comprises a nucleotide sequence of at least 15 contiguous nucleotides that is complementary to at least one functional TCR or Ig V-encoding gene segment and wherein the plurality of V-segment primers specifically hybridize to substantially all functional TCR or Ig V-encoding gene segments that are present in the test sample, and (ii) a plurality of J-segment oligonucleotide primers that are each independently capable of specifically hybridizing to at least one polynucleotide encoding a T cell receptor (TCR) J-region polypeptide or an immunoglobulin (Ig) J-region polypeptide, wherein each J-segment primer comprises a nucleotide sequence of at least 15 contiguous nucleotides that is complementary to at least one functional TCR or Ig J-encoding gene segment and wherein the plurality of J-segment primers specifically hybridize to substantially all functional TCR or Ig J-encoding gene segments that are present in the test sample, wherein the V-segment and J-segment primers are capable of promoting amplification in said multiplex polymerase chain reaction (PCR) of substantially all rearranged TCR or Ig CDR3-encoding regions in the test sample to produce a multiplicity of amplified rearranged DNA molecules from a population of adaptive immune cells in the test sample; and (b) concurrently with said step of amplifying, measuring at one or a plurality of time points a first DNA signal level that is detectable in said multiplicity of amplified rearranged DNA molecules of (a); (c) comparing at said one or plurality of time points the first DNA signal level measured in (b) to a second DNA signal level that is detectable in amplification products of a known amount of control adaptive immune cell template DNA extracted from a control adaptive immune cell sample that has been amplified by the plurality of V-segment oligonucleotide primers and the plurality of J-segment oligonucleotide primers, and therefrom quantifying a relative amount of adaptive immune cell DNA in the test sample template DNA extracted from the test biological sample; and (d) determining, from the relative amount of adaptive immune cell DNA quantified in (c), the relative representation of adaptive immune cell DNA in the test biological sample; and (IV) comparing the relative representation of adaptive immune cell DNA in at least one test biological sample obtained at a time point prior to administering the therapeutic treatment to the relative representation of adaptive immune cell DNA in at least one test biological sample obtained at a time point after administering the therapeutic treatment, and thereby assessing an effect of the therapeutic treatment on relative representation of adaptive immune cells in at least one tissue of a subject.

In certain further embodiments the first and second tissues are the same tissue, and in certain other further embodiments the first and second tissues are different tissues. In certain embodiments of the above described method, step (III) further comprises, for each test biological sample, quantifying a relative amount of DNA in the mixture of cells that comprises adaptive immune cells and cells that are not adaptive immune cells, the method comprising: (e) amplifying test sample template DNA extracted from the test biological sample with a set of control primers to produce internal control gene amplification products, wherein the set of control primers amplifies

12

an internal control gene DNA segment that is not specific to adaptive immune cells; (f) concurrently with step (e), measuring at one or a plurality of time points a third DNA signal level that is detectable in the amplification products of (e); (g) comparing, at said one or plurality of time points, the third DNA signal level in (f) to a fourth DNA signal level that is detectable in amplification products of a known amount of internal control gene DNA that has been amplified by the control primers, and therefrom quantifying a relative amount 10 of internal control gene DNA in the test sample template DNA extracted from the test biological sample; and (h) determining, from the relative amount of internal control gene DNA quantified in (g), the relative amount of DNA in the mixture of cells. In certain embodiments the method assesses a dose-related effect of the therapeutic treatment, wherein a plurality of test biological samples are obtained from the second tissue of the subject at a plurality of time points after administering the therapeutic treatment, and wherein the therapeutic treatment is administered at a plurality of different dosages. In certain embodiments the method assesses a prognosis for the subject receiving the therapeutic treatment, wherein an altered relative representation of adaptive immune cell DNA in at least one test biological sample obtained at a time point after administering the therapeutic treatment compared to the relative representation of adaptive immune cell DNA in at least one test biological sample obtained at a time point prior to administering the therapeutic treatment, indicates an effect of the therapeutic treatment on relative representation of adaptive immune cells in at least one tissue of a subject.

In certain further embodiments the method is selected from: (i) the method in which the subject has cancer and an increased relative representation of adaptive immune cell DNA in at least one test biological sample obtained at a time point after administering the therapeutic treatment compared to the relative representation of adaptive immune cell DNA in at least one test biological sample obtained at a time point prior to administering the therapeutic treatment, indicates a beneficial effect of the therapeutic treatment; (ii) the method in which the subject has an autoimmune disease and a decreased relative representation of adaptive immune cell DNA in at least one test biological sample obtained at a time point after administering the therapeutic treatment compared to the relative representation of adaptive immune cell DNA in at least one test biological sample obtained at a time point prior to administering the therapeutic treatment, indicates a beneficial effect of the therapeutic treatment; and (iii) the method in which the subject has a transplanted organ and a decreased relative representation of adaptive immune cell DNA in at least one test biological sample from the transplanted organ obtained at a time point after administering the therapeutic treatment compared to the relative representation of adaptive immune cell DNA in at least one test biological sample from the transplanted organ obtained at a time point prior to administering the therapeutic treatment, indicates a beneficial effect of the therapeutic treatment. In certain embodiments the method further comprises determining a polynucleotide sequence for each amplified rearranged DNA molecule from the population of adaptive immune cells in the test sample.

In certain other further embodiments the plurality of V-segment oligonucleotide primers and the plurality of J-segment oligonucleotide primers comprise at least one of (1) the sequences set forth in SEQ ID NOS:1-65, (2) the sequences set forth in SEQ ID NOS:67-214, (3) the sequences set forth in SEQ ID NOS:215-238, (4) the sequences set forth in SEQ ID NOS:239-545, (5) the sequences set forth in SEQ ID

13

NOS:546-549 and 634-637, (6) the sequences set forth in SEQ ID NOS:550-633 and 638-643, (7) the sequences set forth in SEQ ID NOS:644-708, (8) the sequences set forth in SEQ ID NOS:644-773, (9) the sequences set forth in SEQ ID NOS:843-879, (10) the sequences set forth in SEQ ID NOS:880-883, and (11) portions of sequences (1) to (10) that are at least 15 nucleotides in length.

In certain other further embodiments either or both of: (i) the V-segment oligonucleotide primers comprise one or a plurality of oligonucleotides that exhibit at least 90% sequence identity to one or more of: (1) the nucleotide sequences set forth in SEQ ID NOS:1-52, (2) the nucleotide sequences set forth in SEQ ID NOS:67-201, (3) the nucleotide sequences set forth in SEQ ID NOS:221-238, (4) the nucleotide sequences set forth in SEQ ID NOS:255-545, (5) the nucleotide sequences set forth in SEQ ID NOS:546-549, (6) the nucleotide sequences set forth in SEQ ID NOS:550-633, (7) the nucleotide sequences set forth in SEQ ID NOS:644-695, (8) the nucleotide sequences set forth in SEQ ID NOS:843-879, and (9) portions of sequences (1) to (8) that are at least 15 nucleotides in length; and (ii) the J-segment primers comprise one or a plurality of oligonucleotides that exhibit at least 90% sequence identity to one or more of: (1) the nucleotide sequences set forth in SEQ ID NOS:53-65, (2) the nucleotide sequences set forth in SEQ ID NOS:202-214, (3) the nucleotide sequences set forth in SEQ ID NOS:215-220, (4) the nucleotide sequences set forth in SEQ ID NOS:239-254, (5) the nucleotide sequences set forth in SEQ ID NOS:634-637, (6) the nucleotide sequences set forth in SEQ ID NOS:638-643, (7) the nucleotide sequences set forth in SEQ ID NOS:696-708, (8) the nucleotide sequences set forth in SEQ ID NO:880-883, and (9) portions of sequences (1) to (8) that are at least 15 nucleotides in length.

These and other aspects of the herein described invention embodiments will be evident upon reference to the following detailed description and attached drawings. All of the U.S. patents, U.S. patent application publications, U.S. patent applications, foreign patents, foreign patent applications and non-patent publications referred to in this specification and/or listed in the Application Data Sheet are incorporated herein by reference in their entirety, as if each was incorporated individually. Aspects and embodiments of the invention can be modified, if necessary, to employ concepts of the various patents, applications and publications to provide yet further embodiments.

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS

FIGS. 1A and 1B show quantitative PCR determination of the relative representation of T cell DNA in total DNA extracted from a tumor sample containing tumor infiltrating lymphocytes (TIL). FIG. 1A shows an amplification profile; FIG. 1B shows a standard curve generated from known amounts of peripheral blood T cell DNA, as used to extrapolate T cell concentrations in complex cell mixtures of peripheral blood and tissue DNA.

FIG. 2 is a schematic presentation of a PCR assay (e.g., a qPCR assay or a dPCR assay).

FIG. 3 shows dPCR results using TCRV18, TCRV19 or RNase P specific probes and buffy coat DNA as the template. Each data point represents a single dPCR specific reaction for the V18, V19, or RNase P specific probe. Droplets are assigned as positive (above horizontal separation lines) or negative (below horizontal separation lines) based on their fluorescence amplitude. The number of positive and negative droplets in each channel is used to calculate the concentration

14

of target molecules and the Poisson-based confidence intervals to enumerate the V gene segment-specific T lymphocyte population (0.6% for the V18 segment and 1.2% for the V19 segment).

FIG. 4 shows an exemplary assay plate for using dPCR to quantify tumor infiltrating lymphocytes in samples.

FIGS. 5A-5C show dPCR results using eight different subgroups of probes and primers (A through H). Each data point represents a single dPCR specific reaction for the probes of subgroups A through H. Droplets were assigned as positive (above horizontal separation lines) or negative (below horizontal separation lines) based on their fluorescence amplitude. The number of positive and negative droplets in each channel was used to calculate the concentration of target molecules and the Poisson-based confidence intervals to enumerate the V gene segment-specific T lymphocyte population. FIG. 5A shows dPCR T cell quantification using subgroups A-H by detection of rearranged TCR genes in template DNA from peripheral blood lymphocytes from a healthy donor. FIG. 5B shows dPCR T cell quantification by detecting TCR rearrangements when template DNA was obtained from a bone marrow sample obtained from a T-ALL patient (79.7% for the subgroup A segment, which was a pattern characteristic of the disease state of the patient). FIG. 5C shows dPCR T cell quantification results when template DNA was obtained from a patient with ETP T-ALL, characterized by a primary T cell clone that has not undergone TCR encoding DNA rearrangement.

FIG. 6 is a graph showing low variation in TIL percentage and clonality in three different biopsies from a large cervical tumor. Shading represents percentage of TIL identified with indicated pooled primer subgroup.

FIG. 7 is a graph showing that an assay measuring RNaseP+ cell concentrations using dPCR was accurate across a large dynamic range (from 1 to 10^4 RNaseP+ cells per well).

DETAILED DESCRIPTION

According to certain embodiments as described herein there is provided a highly sensitive and accurate method for determining the relative representation of adaptive immune cells in a biological sample that contains a mixture of cells, where the mixture comprises adaptive immune cells as provided herein, and also comprises cells that are not adaptive immune cells.

Based on the present disclosure, the relative representation of DNA from adaptive immune cells (e.g., T and/or B lymphocytes having rearranged adaptive immune receptor genes, including T- and B-lineage cells of different maturational stages such as precursors, blast cells, progeny or the like) in DNA from a sample of mixed cell types may be quantified. For instance, certain embodiments permit determination, in DNA extracted from a biological sample, of the relative representation of DNA from tumor infiltrating lymphocytes (TIL) in the DNA from the biological sample, where the sample comprises all or a portion of a tumor that contains adaptive immune cells and cells that are not adaptive immune cells (including tumor cells). Certain other embodiments, for example, permit determination, in DNA extracted from a biological sample, of the relative representation of DNA from infiltrating lymphocytes in the DNA from the biological sample, where the sample comprises all or a portion of a somatic tissue that contains adaptive immune cells and cells that are not adaptive immune cells, such as cells of a solid tissue.

15

In certain embodiments, as described herein and according to non-limiting theory, rearranged adaptive immune cell DNA is amplified in real time quantitative PCR using rearranged adaptive immune receptor-specific oligonucleotide primer sets to quantify an adaptive immune cell-specific DNA signal that may be used as a marker for the relative contribution of adaptive immune cells to the total DNA that is extracted from a sample of mixed cell types. The present embodiments therefore provide quantitative determination of the relative representation of adaptive immune cell DNA in a DNA sample extracted from a mixture of cells. The cells in the mixture of cells may not all be adaptive immune cells, and certain unforeseen advantages of the herein described embodiments are obtained where the cells in the mixture of cells need not all be adaptive immune cells. As described herein, compositions and methods are provided for quantifying the proportion of cellular genomes in a DNA sample that are contributed by adaptive immune cells relative to the total number of cellular genomes in the sample, starting from a DNA sample that has been extracted from a mixture of cell types, such as a solid tumor or a solid tissue.

Further according to non-limiting theory, the present embodiments exploit the capability, in a real time quantitative polymerase chain reaction (qPCR), that is afforded by oligonucleotide primer sets that specifically amplify substantially all rearranged adaptive immune receptor genes (e.g., CDR3 encoding polynucleotide-containing portions of rearranged T cell receptor and/or immunoglobulin genes) that may be present in a DNA sample, to generate a first detectable DNA signal that quantitatively reflects the production of a multiplicity of amplified rearranged adaptive immune receptor encoding DNA molecules. A second detectable DNA signal is generated, using the same oligonucleotide primer sets, in qPCR from a known amount of adaptive immune cell template DNA (e.g., sourced from a known number of adaptive immune cells or a known number of adaptive immune cell genomes), to produce a calibration curve, from which the relative amount of adaptive immune cell DNA reflected in the first detectable DNA signal can be determined.

Certain related embodiments may further include qPCR amplification and detection of a third detectable DNA signal that quantitatively reflects the production of a multiplicity of amplified DNA molecules, using template DNA extracted from the mixture of cells with oligonucleotide primers that amplify an internal control gene that is present in adaptive immune cells and in cells that are not adaptive immune cells, and generation of a fourth detectable DNA signal using such primers in qPCR amplification of a known amount of template internal control gene DNA, to produce a calibration curve from which the relative amount of DNA in the cell mixture and hence the number of cellular genomes (e.g., cell number) can be determined.

In another embodiment, the present disclosure provides a method for quantifying the relative representation of adaptive immune cells in a test biological sample using digital polymerase chain reaction (dPCR). Substantially all rearranged adaptive immune cell DNA is amplified in dPCR using rearranged adaptive immune receptor-specific oligonucleotide primer sets. The number of assay samples that detectably contain rearranged DNA amplified using diluted DNA from the test biological sample of interest as templates is compared to the number of assay samples that detectably contain an internal control gene amplified using the same diluted DNA as templates. Because the copy number of the internal control gene is known (e.g., 2), the relative representation of adaptive immune cells in the test biological sample (e.g., percentage of

16

the total cells in the test biological sample that are adaptive immune cells) may be determined from the above comparison.

The present invention is thus directed in certain embodiments as described herein to quantification of DNA from adaptive immune cells that are present in solid tissues, and in particular embodiments, to solid tumors, such that the relative presence of adaptive immune cells as a proportion of all cell types that may be present in the tissue (e.g., tumor) can be determined. These and related embodiments are in part a result of certain surprising and heretofore unrecognized advantages disclosed in greater detail below that derive from exquisite sensitivity that is afforded, for the detection of adaptive immune cells, by the design of multiplexed qPCR or multiplexed dPCR using the herein described oligonucleotide primer sets. These primer sets permit production of amplified rearranged DNA molecules that encode portions of adaptive immune receptors. These and related embodiments feature the selection of a plurality of oligonucleotide primers that specifically hybridize to adaptive immune receptor (e.g., T cell receptor, TCR; or immunoglobulin, Ig) V-region polypeptide encoding polynucleotide sequences and J-region polypeptide encoding polynucleotide sequences. The primers promote qPCR amplification of DNA molecules that include substantially all rearranged TCR CDR3-encoding or Ig CDR3-encoding gene regions that may be present in a test biological sample, where the sample contains a mixture of cells which comprises adaptive immune cells (e.g., T- and B-lymphocyte lineage cells) and cells that are not adaptive immune cells. For example, a cell mixture may be obtained from a solid tumor that comprises tumor cells and TIL.

In certain embodiments, qPCR amplification may be monitored at one or a plurality of time points during the course of the qPCR reaction, i.e., in "real time". Real-time monitoring permits determination of the quantity of DNA that is being generated by comparing a so-measured adaptive immune receptor-encoding DNA-quantifying signal to an appropriate control DNA-quantifying signal, which may be used as a calibration standard.

In certain other embodiments, rearranged adaptive immune cell DNA is quantified by dPCR. The DNA isolated from a test biological sample is distributed to form a set of assay samples, and the reaction is carried out in each assay sample individually. After the amplification, each assay sample produces either a negative result (i.e., no rearranged adaptive immune cell DNA is amplified) or a positive result (i.e., rearranged adaptive immune cell DNA is amplified). The amount of rearranged adaptive immune cell DNA may be quantified by counting the number of assay samples that produce positive results. For dPCR, the amplification process does not need to be monitored (as opposed to real time qPCR), which eliminates the reliance on uncertain exponential data to quantify target nucleic acid as in real time qPCR. In addition, dPCR does not require a calibration curve produced by amplifying a known amount of adaptive immune cell template DNA. Instead, dPCR amplifies an internal control (e.g., "housekeeping") gene that is present in adaptive immune cells and in cells that are not adaptive immune cells, which allows the determination of the total numbers of cells from which the template DNA is extracted.

In certain embodiments, a test biological sample of interest comprises somatic tissue. The somatic tissue may comprise a solid tissue that is a site for autoimmune disease pathology, such as a tissue that is inappropriately targeted by a host's immune system for an "anti-self" immune response. In certain other embodiments, the somatic tissue may comprise a solid tissue that is a site of an infection, such as a bacterial,

yeast, viral or other microbial infection, for example, a Herpes Simplex Virus (HSV) infection. In yet other embodiments, the somatic tissue is from a transplanted organ (e.g., a transplanted liver, lung, kidney, heart, spleen, pancreas, skin, intestine and thymus). These and related embodiments, as described in greater detail below, will find uses in diagnostic, prognostic, disease monitoring, therapeutic efficacy monitoring and other contexts, thereby providing important information, such as quantification of adaptive immune cell representation in complex tissues that comprise a mixture of cell types. Adaptive immune cell quantification (e.g., quantification of the relative representation of adaptive immune cells in samples) or adaptive immune cell DNA quantification (e.g., quantification of the relative representation of adaptive immune cell DNA in samples that contain DNA from a mixture of cells) in tissues before and after, and/or during the course of treatment of a subject, will usefully provide information of relevance to the diagnosis and prognosis in patients having cancer, inflammation and/or autoimmune disease, or any of a number of other conditions that may be characterized by alterations (e.g., statistically significant increases or decreases) in adaptive immune cell presence in one or more tissues.

As provided herein, the relative representation of adaptive immune cells or their DNA may be quantified in adaptive immune cells or their DNA obtained from a test biological sample that contains a mixture of cells, including adaptive immune cells and cells that are not adaptive immune cells, where the test sample is obtained from a solid tissue in a subject such as a solid tumor, prior to, during and/or following administration of a therapeutic regimen to the subject. A test biological sample may be obtained, for example, by excision of tissue from a pre- or post-treatment subject.

Adaptive immune cell quantification or adaptive immune cell DNA quantification as an indicator of the relative presence of adaptive immune cells in a mixed cell population as described herein may, in certain embodiments, optionally be accompanied by evaluation or analysis of the tissue according to other art-accepted criteria. Indicators of status (e.g., evidence of presence or absence of pathology, or of efficacy of a previously or contemporaneously administered therapeutic treatment) may be, for example, detectable indicator compounds, nanoparticles, nanostructures or other compositions that comprise a reporter molecule which provides a detectable signal indicating the physiological status of a cell or tissue, such as a vital dye (e.g., Trypan blue), a colorimetric pH indicator, a fluorescent compound that may exhibit distinct fluorescence as a function of any of a number of cellular physiological parameters (e.g., pH, intracellular Ca²⁺ or other physiologically relevant ion concentration, mitochondrial membrane potential, plasma membrane potential, etc., see Haugland, *The Handbook: A Guide to Fluorescent Probes and Labeling Technologies* (10th Ed.) 2005, Invitrogen Corp., Carlsbad, Calif.), an enzyme substrate, a specific oligonucleotide probe, a reporter gene, or the like.

Certain embodiments contemplate comparison of relative adaptive immune cell DNA quantities in view of total cell DNA (e.g., from adaptive immune cells plus non-adaptive immune cells in the cell mixture) and optionally other relevant parameters before, during or after administration to a control subject of control compositions that may be, for example, negative controls that have been previously demonstrated to have undergone no statistically significant alteration of physiological state, such as sham injection, saline, DMSO or other vehicle or buffer control, inactive enantiomers, scrambled peptides or nucleotides, etc.; and/or before, during or after administration of positive controls that have

been previously demonstrated to cause a statistically significant alteration of physiological state, such as an FDA-approved therapeutic compound.

The subject or biological source, from which a test biological sample may be obtained, may be a human or non-human animal, or a transgenic or cloned or tissue-engineered (including through the use of stem cells) organism. In certain preferred embodiments of the invention, the subject or biological source may be known to have, or may be suspected of having or being at risk for having, a solid tumor or other malignant condition, or an autoimmune disease, or an inflammatory condition, and in certain preferred embodiments of the invention the subject or biological source may be known to be free of a risk or presence of such disease.

Certain preferred embodiments contemplate a subject or biological source that is a human subject such as a patient that has been diagnosed as having or being at risk for developing or acquiring cancer according to art-accepted clinical diagnostic criteria, such as those of the U.S. National Cancer Institute (Bethesda, Md., USA) or as described in *DeVita, Hellman, and Rosenberg's Cancer: Principles and Practice of Oncology* (2008, Lippincott, Williams and Wilkins, Philadelphia/Ovid, New York); Pizzo and Poplack, *Principles and Practice of Pediatric Oncology* (Fourth edition, 2001, Lippincott, Williams and Wilkins, Philadelphia/Ovid, New York); and Vogelstein and Kinzler, *The Genetic Basis of Human Cancer* (Second edition, 2002, McGraw Hill Professional, New York); certain embodiments contemplate a human subject that is known to be free of a risk for having, developing or acquiring cancer by such criteria.

Certain other embodiments contemplate a non-human subject or biological source, for example a non-human primate such as a macaque, chimpanzee, gorilla, vulture, orangutan, baboon or other non-human primate, including such non-human subjects that may be known to the art as preclinical models, including preclinical models for solid tumors and/or other cancers. Certain other embodiments contemplate a non-human subject that is a mammal, for example, a mouse, rat, rabbit, pig, sheep, horse, bovine, goat, gerbil, hamster, guinea pig or other mammal; many such mammals may be subjects that are known to the art as preclinical models for certain diseases or disorders, including solid tumors and/or other cancers (e.g., Talmadge et al., 2007 *Am. J. Pathol.* 170:793; Kerbel, 2003 *Canc. Biol. Therap.* 2(4 Suppl 1):S134; Man et al., 2007 *Canc. Met. Rev.* 26:737; Cespedes et al., 2006 *Clin. Transl. Oncol.* 8:318). The range of embodiments is not intended to be so limited, however, such that there are also contemplated other embodiments in which the subject or biological source may be a non-mammalian vertebrate, for example, another higher vertebrate, or an avian, amphibian or reptilian species, or another subject or biological source.

Biological samples may be provided by obtaining a blood sample, biopsy specimen, tissue explant, organ culture, biological fluid or any other tissue or cell preparation from a subject or a biological source. In certain preferred embodiments a test biological sample may be obtained from a solid tissue (e.g., a solid tumor), for example by surgical resection, needle biopsy or other means for obtaining a test biological sample that contains a mixture of cells.

Solid tissues are well known to the medical arts and may include any cohesive, spatially discrete non-fluid defined anatomic compartment that is substantially the product of multicellular, intercellular, tissue and/or organ architecture, such as a three-dimensionally defined compartment that may comprise or derive its structural integrity from associated connective tissue and may be separated from other body areas by a thin membrane (e.g., meningeal membrane, pericardial mem-

brane, pleural membrane, mucosal membrane, basement membrane, omentum, organ-encapsulating membrane, or the like). Non-limiting exemplary solid tissues may include brain, liver, lung, kidney, prostate, ovary, spleen, lymph node (including tonsil), skin, thyroid, pancreas, heart, skeletal muscle, intestine, larynx, esophagus and stomach. Anatomical locations, morphological properties, histological characterization, and invasive and/or non-invasive access to these and other solid tissues are all well known to those familiar with the relevant arts.

Solid tumors of any type are contemplated as being suitable for characterization of TIL using the compositions and methods described herein. In certain preferred embodiments, the solid tumor may be a benign tumor or a malignant tumor, which may further be a primary tumor, an invasive tumor or a metastatic tumor. Certain embodiments contemplate a solid tumor that comprises one of a prostate cancer cell, a breast cancer cell, a colorectal cancer cell, a lung cancer cell, a brain cancer cell, a renal cancer cell, a skin cancer cell (such as squamous cell carcinoma, basal cell carcinoma, or melanoma) and an ovarian cancer cell, but the invention is not intended to be so limited and other solid tumor types and cancer cell types may be used. For example, the tumor may comprise a cancer selected from adenoma, adenocarcinoma, squamous cell carcinoma, basal cell carcinoma, melanoma (e.g., malignant melanoma), small cell carcinoma, large cell undifferentiated carcinoma, chondrosarcoma and fibrosarcoma, or the like. As also noted elsewhere herein, art-accepted clinical diagnostic criteria have been established for these and other cancer types, such as those promulgated by the U.S. National Cancer Institute (Bethesda, Md., USA) or as described in *DeVita, Hellman, and Rosenberg's Cancer: Principles and Practice of Oncology* (2008, Lippincott, Williams and Wilkins, Philadelphia/Ovid, New York); Pizzo and Poplack, *Principles and Practice of Pediatric Oncology* (Fourth edition, 2001, Lippincott, Williams and Wilkins, Philadelphia/Ovid, New York); and Vogelstein and Kinzler, *The Genetic Basis of Human Cancer* (Second edition, 2002, McGraw Hill Professional, New York). Other non-limiting examples of typing and characterization of particular cancers are described, e.g., in Ignatiadis et al. (2008 *Pathobiol.* 75:104); Kunz (2008 *Curr. Drug Discov. Technol.* 5:9); and Auman et al. (2008 *Drug Metab. Rev.* 40:303).

Accordingly, described herein are methods for measuring the number of adaptive immune cells, particularly T cells, in a complex mixture of cells. The present methods have particular utility in quantifying tumor-infiltrating lymphocytes or lymphocytes infiltrating somatic tissue that is the target of an autoimmune response. Existing methods for T and B cell quantification rely upon the physical separation of such cells from the mixture. However, in many cases, T and B cells cannot be separated from the initial sample, such as formalin-fixed or frozen tissue samples. Furthermore, prior methods for adaptive immune cell quantification (e.g., flow immunocytofluorimetry, fluorescence activated cell sorting (FACS), immunohistochemistry (IHC)) rely on the expression of T cell- or B cell-specific proteins, such as cell surface receptors. Since immune cells express varying amounts of these lineage specific receptors, quantifying the number of cells from such a highly variable measure requires costly standardization, specialized equipment and highly trained staff. The presently disclosed methods are, by contrast, platform-independent and can be performed on any real-time PCR instrument or dPCR instrument, and the reagents can be synthesized and provided in kit form. The presently disclosed methods are also highly sensitive and can be applied in high throughput settings not previously attainable. As described herein, quantification of

adaptive immune cells may be achieved by a simple preparation of DNA from a complex mixture of cells, in concert with quantification of the relative proportion of adaptive immune cells present by amplification of the uniquely rearranged adaptive immune cell CDR3-encoding genes.

According to certain embodiments, a method for quantification of the relative contribution to total DNA in a sample that is made by DNA from adaptive immune cells in a test biological sample that contains a mixture of cells (only some of which are adaptive immune cells) by qPCR analysis of amplified (using the herein described V- and J-specific primer sets) rearranged V-segments and J-segments from the adaptive immune cell contribution to the DNA extracted from the test sample, may also comprise qPCR analysis of amplified rearranged V- and J-segments amplified (using the same V- and J-primer sets) from DNA extracted from a control adaptive immune cell sample that comprises a known number of adaptive immune cells. The control adaptive immune cell sample comprises a population of pure or substantially pure (e.g., greater than at least 70%, 75%, 80%, 85%, 90%, 95%, 97%, 98% or 99%) adaptive immune cells that may be obtained from a subject or biological source as provided herein. Amplification from a known amount of such control adaptive immune cell DNA that is used as a starting template, and measurement in qPCR of rearranged V-J-encoding amplification products, will permit the generation of a calibration curve from which to determine the quantity of amplified rearranged DNA molecules that are produced in the qPCR from a known number of adaptive immune cells. From such a calibration curve, the quantity of amplified rearranged DNA that is produced from the test biological sample may be compared, and from that quantity the number of adaptive immune cells in the test biological sample may be determined.

B cells and T cells can thus be obtained, for use as a control adaptive immune cell sample, from a biological sample, such as from a variety of tissue and biological fluid samples including bone marrow, thymus, lymph glands, lymph nodes, peripheral tissues and blood, but peripheral blood is most easily accessed. Any peripheral tissue can be sampled for the presence of B and T cells and is therefore contemplated for use in the methods described herein. Tissues and biological fluids from which adaptive immune cells, for use in a control adaptive immune cell sample, may be obtained include, but are not limited to skin, epithelial tissues, colon, spleen, a mucosal secretion, oral mucosa, intestinal mucosa, vaginal mucosa or a vaginal secretion, cervical tissue, ganglia, saliva, cerebrospinal fluid (CSF), bone marrow, cord blood, serum, serosal fluid, plasma, lymph, urine, ascites fluid, pleural fluid, pericardial fluid, peritoneal fluid, abdominal fluid, culture medium, conditioned culture medium or lavage fluid. In certain embodiments, adaptive immune cells may be isolated from an apheresis sample. Peripheral blood samples may be obtained by phlebotomy from subjects. Peripheral blood mononuclear cells (PBMC) are isolated by techniques known to those of skill in the art, e.g., by Ficoll-Hypaque® density gradient separation. In certain embodiments, whole PBMCs are used for analysis.

In certain related embodiments, preparations that comprise predominantly lymphocytes (e.g., T and B cells) or that comprise predominantly T cells or predominantly B cells, may be prepared for use as a control adaptive immune cell sample as provided herein, according to established, art-accepted methodologies. In other related embodiments, specific subpopulations of T or B cells may be isolated prior to analysis using the methods described herein. Various methods and commercially available kits for isolating different subpopulations of T and B cells are known in the art and include, but are not

limited to, subset selection immunomagnetic bead separation or flow immunocytometric cell sorting using antibodies specific for one or more of any of a variety of known T and B cell surface markers. Illustrative markers include, but are not limited to, one or a combination of CD2, CD3, CD4, CD8, CD14, CD19, CD20, CD25, CD28, CD45RO, CD45RA, CD54, CD62, CD62L, CDw137 (41BB), CD154, GITR, FoxP3, CD54, and CD28. For example, and as is known to the skilled person, cell surface markers, such as CD2, CD3, CD4, CD8, CD14, CD19, CD20, CD45RA, and CD45RO may be used to determine T, B, and monocyte lineages and subpopulations in flow cytometry. Similarly, forward light-scatter, side-scatter, and/or cell surface markers such as CD25, CD62L, CD54, CD137, CD154 may be used to determine activation state and functional properties of cells.

Illustrative combinations useful in certain of the methods described herein may include CD8⁺CD45RO³⁰ (memory cytotoxic T cells), CD4⁺CD45RO⁺ (memory T helper), CD8⁺CD45RO⁻ (CD8⁺CD62L^{+CD}45RA⁺ (naive-like cytotoxic T cells); CD4⁺CD25⁺CD62L^{hi}GITR^{+FoxP3+} (regulatory T cells). Illustrative antibodies for use in immunomagnetic cell separations or flow immunocytometric cell sorting include fluorescently labeled anti-human antibodies, e.g., CD4 FITC (clone M-T446, Miltenyi Biotec), CD8 PE (clone RPA-T8, BD Biosciences), CD45RO ECD (clone UCHL-1, Beckman Coulter), and CD45 RO APC (clone UCHL-1, Biosciences). Staining of total PBMC's may be done with the appropriate combination of antibodies, followed by washing cells before analysis. Lymphocyte subsets can be isolated by fluorescence activated cell sorting(FACS), e.g., by a BD FACSARIA™ cell-sorting system (BD Biosciences) and by analyzing results with FLOWJO™ software (Treestar Inc.), and also by conceptually similar methods involving specific antibodies immobilized to surfaces or beads.

For nucleic acid extraction, total genomic DNA may be extracted from cells using methods known in the art and/or commercially available kits, e.g., by using the QIAAMP® DNA blood Mini Kit (QIAGEN®). The approximate mass of a single haploid genome is 3 pg. Preferably, at least 100,000 to 200,000 cells are used for analysis, i.e., about 0.6 to 1.2 µg DNA from diploid T or B cells. Using PBMCs as a source, the number of T cells can be estimated to be about 30% of total cells. The number of B cells can also be estimated to be about 30% of total cells in a PBMC preparation.

Adaptive Immune Cell Receptors

The native TCR is a heterodimeric cell surface protein of the immunoglobulin superfamily which is associated with invariant proteins of the CD3 complex involved in mediating signal transduction. TCRs exist in αβ and γδ forms, which are structurally similar but have quite distinct anatomical locations and probably functions. The MHC class I and class II ligands, which bind to the TCR, are also immunoglobulin superfamily proteins but are specialized for antigen presentation, with a highly polymorphic peptide binding site which enables them to present a diverse array of short peptide fragments at the APC cell surface.

The extracellular portions of native heterodimeric αβ and γδ TCRs consist of two polypeptides each of which has a membrane-proximal constant domain, and a membrane-distal variable domain. Each of the constant and variable domains includes an intra-chain disulfide bond. The variable domains contain the highly polymorphic loops analogous to the complementarity determining regions (CDRs) of antibodies. CDR3 of αβ TCRs interact with the peptide presented by MHC, and CDRs 1 and 2 of αβ TCRs interact with the peptide and the MHC. The diversity of TCR sequences is generated

via somatic rearrangement of linked variable (V), diversity (D), joining (J), and constant genes.

The Ig and TCR gene loci contain many different variable (V), diversity (D), and joining (J) gene segments, which are subjected to rearrangement processes during early lymphoid differentiation. Ig and TCR V, D and J gene segment sequences are known in the art and are available in public databases such as GENBANK. TCRB V region gene segment sequences are set forth in the sequence listing at SEQ ID NOS:1-52, 66-201, 644-695, 709-839, and 843-879, and the TCRB J region segment sequences are set forth in SEQ ID NOS:53-65, 202-214, 696-708, and 880-883. TCRG J region gene segment sequences are set forth in SEQ ID NOS:215-220 and 634-637. TCRG V region gene segment sequences are set forth in SEQ ID NOS:221-238 and 546-549. IgH J region gene segment sequences are set forth in SEQ ID NOS:239-254 and 638-643; IgHV region gene segment sequences are set forth in SEQ ID NOS:255-255 and 550-633.

The V-D-J rearrangements are mediated via a recombinase enzyme complex in which the RAG1 and RAG2 proteins play a key role by recognizing and cutting the DNA at the recombination signal sequences (RSS), which are located downstream of the V gene segments, at both sides of the D gene segments, and upstream of the J gene segments. Inappropriate RSS reduce or even completely prevent rearrangement. The recombination signal sequence (RSS) consists of two conserved sequences (heptamer, 5'-CACAGTG-3', and nonamer, 5'-ACAAAAACC-3'), separated by a spacer of either 12/+/-1 bp ("12-signal") or 23/+/-1 bp ("23-signal"). A number of nucleotide positions have been identified as important for recombination including the CA dinucleotide at position one and two of the heptamer, and a C at heptamer position three has also been shown to be strongly preferred as well as an A nucleotide at positions 5, 6, 7 of the nonamer. (Ramsden et al. 1994 *Nucl. Ac. Res.* 22:1785; Akamatsu et al. 1994 *J. Immunol.* 153:4520; Hesse et al. 1989 *Genes Dev.* 3:1053). Mutations of other nucleotides have minimal or inconsistent effects. The spacer, although more variable, also has an impact on recombination, and single-nucleotide replacements have been shown to significantly impact recombination efficiency (Fanning et al. 1996 *Cell. Immunol. Immunopath.* 79:1; Larijani et al. 1999 *Nucl. Ac. Res.* 27:2304; Nadel et al. 1998 *J. Immunol.* 161:6068; Nadel et al. 1998 *J. Exp. Med.* 187:1495). Criteria have been described for identifying RSS polynucleotide sequences having significantly different recombination efficiencies (Ramsden et al. 1994 *Nucl. Ac. Res.* 22:1785; Akamatsu et al. 1994 *J. Immunol.* 153:4520; Hesse et al. 1989 *Genes Dev.* 3:1053, and Lee et al., 2003 *PLoS 1*(1):E1).

The rearrangement process generally starts with a D to J rearrangement followed by a V to D-J rearrangement in the case of Ig heavy chain (IgH), TCR beta (TCRB), and TCR delta (TCRD) genes or concerns direct V to J rearrangements in case of Ig kappa (IgK), Ig lambda (IgL), TCR alpha (TCRA), and TCR gamma (TCRG) genes. The sequences between rearranging gene segments are generally deleted in the form of a circular excision product, also called TCR excision circle (TREC) or B cell receptor excision circle (BREC).

The many different combinations of V, D, and J gene segments represent the so-called combinatorial repertoire, which is estimated to be ~2×10⁶ for Ig molecules, ~3×10⁶ for TCRαβ and ~5×10³ for TCRγδ molecules. At the junction sites of the V, D, and J gene segments, deletion and random insertion of nucleotides occurs during the rearrangement process, resulting in highly diverse junctional regions, which

significantly contribute to the total repertoire of Ig and TCR molecules, estimated to be $>10^{12}$.

Mature B-lymphocytes further extend their Ig repertoire upon antigen recognition in follicle centers via somatic hypermutation, a process, leading to affinity maturation of the Ig molecules. The somatic hypermutation process focuses on the V- (D-) J exon of IgH and Ig light chain genes and concerns single nucleotide mutations and sometimes also insertions or deletions of nucleotides. Somatically-mutated Ig genes are also found in mature B-cell malignancies of follicular or post-follicular origin.

In certain preferred embodiments described herein, V-segment and J-segment primers may be employed in a qPCR reaction or a dPCR reaction to amplify rearranged TCR or Ig CDR3-encoding DNA regions in a test biological sample, wherein each functional TCR or Ig V-encoding gene segment comprises a V gene recombination signal sequence (RSS) and each functional TCR or Ig J-encoding gene segment comprises a J gene RSS. In these and related embodiments, each amplified rearranged DNA molecule may comprise (i) at least about 10, 20, 30 or 40 contiguous nucleotides of a sense strand of the TCR or Ig V-encoding gene segment, with the at least about 10, 20, 30 or 40 contiguous nucleotides being situated 5' to the V gene RSS and/or each amplified rearranged DNA molecule may comprise (ii) at least about 10, 20 or 30 contiguous nucleotides of a sense strand of the TCR or Ig J-encoding gene segment, with the at least about 10, 20 or 30 contiguous nucleotides being situated 3' to the J gene RSS.

Multiplex Quantitative PCR

As described herein there is provided a method for quantifying the relative representation of adaptive immune cell DNA in DNA from a test biological sample of mixed cell types, and thus for estimating the relative number of T or B cells in a complex mixture of cells. According to certain embodiments, the method involves a multiplex PCR method using a set of forward primers that specifically hybridize to the V segments and a set of reverse primers that specifically hybridize to the J segments where the multiplex PCR reaction allows amplification of all the possible VJ (and VDJ) combinations within a given population of T or B cells. Because the multiplex PCR reaction amplifies substantially all possible combinations of V and J segments, it is possible to determine, using real-time quantitative PCR, the relative number of T cell or B cell genomes in a sample comprising a mixed population of cells. In particular, in order to measure the relative number of TCR or BCR genomes, it is assumed that there is 3 pg DNA per genome, or 6 pg per diploid cell. Once the amount of starting DNA is calculated using real-time qPCR with appropriate standards/controls as described further herein, from this number it is possible to calculate the number of TCR or BCR genomes. A standard DNA dilution panel of TCR genomes is used as a control to determine the amount of DNA in pg or μ g in a given sample.

DNA or RNA may be extracted from a mixed population of cells from a sample, such as any neoplastic tissue sample or a sample of somatic tissue that is the target of an autoimmune reaction, blood sample, or cerebrospinal fluid, using standard methods or commercially available kits known in the art. Illustrative samples for use in the present methods include any type of solid tumor, in particular, from colorectal, hepatocellular, gallbladder, pancreatic, esophageal, lung, breast, prostate, head and neck, renal cell carcinoma, ovarian, endometrial, cervical, bladder and urothelial cancers. Any solid tumor in which tumor-infiltrating lymphocytes are to be assessed is contemplated for use in the present methods. Somatic tissues that are the target of an autoimmune reaction that are contemplated for analysis using the methods herein

include, but are not limited to, joint tissues, skin, intestinal tissue, all layers of the uvea, iris, vitreous tissue, heart, brain, lungs, blood vessels, liver, kidney, nerve tissue, muscle, spinal cord, pancreas, adrenal gland, tendon, mucus membrane, lymph node, thyroid, endometrium, connective tissue, and bone marrow. In certain embodiments, DNA or RNA may be extracted from a transplanted organ, such as a transplanted liver, lung, kidney, heart, spleen, pancreas, skin, intestine, and thymus.

In certain embodiments, two or more samples may be obtained from a single tissue (e.g., a single neoplastic tissue) and the relative representations of adaptive immune cells in the two or more samples are quantified to consider variations in different sections of a test tissue. In certain other embodiments, the determination of the relative representation of adaptive immune cells in one sample from a test tissue is sufficient due to minimum variations among different sections of the test tissue (see, e.g., Example 8).

A multiplex PCR system may be used to amplify rearranged adaptive immune cell receptor loci from genomic DNA, preferably from a CDR3 region. In certain embodiments, the CDR3 region is amplified from a TCR α , TCR β , TCR γ or TCR δ CDR3 region or similarly from an IgH or IgL (lambda or kappa) locus.

Compositions are provided that comprise a plurality of V-segment and J-segment primers that are capable of promoting amplification in a multiplex polymerase chain reaction (PCR) of substantially all productively rearranged adaptive immune receptor CDR3-encoding regions in the sample for a given class of such receptors (e.g., TCR γ , TCR β , IgH, etc.), to produce a multiplicity of amplified rearranged DNA molecules from a population of T cells (for TCR) or B cells (for Ig) in the sample.

Preferably and in certain embodiments, primers are designed so that each amplified rearranged DNA molecule in the multiplicity of amplified rearranged DNA molecules is less than 600 nucleotides in length, thereby excluding amplification products from non-rearranged adaptive immune receptor loci. An exemplary schematic presentation of a qPCR assay (which may also serve as a schematic presentation of a dPCR assay) is shown in FIG. 2. The PCR assay uses forward primers and TaqMan® probes in each V segment and reverse primers in each J segment to selectively amplify the rearranged VDJ from each cell. While these primers can anneal to both rearranged and germline V and J gene segments, PCR amplification is limited to rearranged gene segments, due to size bias (e.g., 250 bp PCR product using rearranged gene segments as templates vs >10 Kb PCR product using germline gene segments as templates).

In the human genome there are currently believed to be about 70 TCR V α and about 61 J α gene segments, about 52 TCR V β , about 2 D β and about 13 J β gene segments, about 9 TCR V γ and about 5 J γ gene segments, and about 46 immunoglobulin heavy chain (IGH) V H , about 23 D H and about 6 J H gene segments. Accordingly, where genomic sequences for these loci are known such that specific molecular probes for each of them can be readily produced, it is believed according to non-limiting theory that the present compositions and methods relate to substantially all (e.g., greater than 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99%) of these known and readily detectable adaptive immune receptor V-, D- and J-region encoding gene segments.

Primer selection and primer set design may be performed according to certain embodiments in a manner that preferably detects productive V and J gene segments, for example, by excluding TCR or Ig pseudogenes. Pseudogenes may include V segments that contain an in-frame stop codon within the

V-segment coding sequence, a frameshift between the start codon and the CDR3 encoding sequence, one or more repeat-element insertions, and deletions of critical regions, such as the first exon or the RSS. In the human IGH locus, for instance, the ImmunoGeneTics (IMGT) database (M.-P. LeFranc, Université Montpellier, Montpellier, France; www.imgt.org) annotates 165 V segment genes, of which 26 are orphans on other chromosomes and 139 are in the IGH locus at chromosome 14. Among the 139 V segments within the IGH locus, 51 have at least one functional allele, while 6 are ORFs (open-reading frames) which are missing at least one highly conserved amino-acid residue, and 81 are pseudogenes.

To detect functional TCR or IG rearrangements in a sample while avoiding potentially extraneous amplification signals that may be attributable to non-productive V and/or J gene segments such as pseudogenes and/or orphans, it is therefore contemplated according to certain embodiments to use a subset of oligonucleotide primers which is designed to include only those V segments that participate in a functional rearrangement to encode a TCR or IG, without having to include amplification primers specific to the pseudogene and/or orphon sequences or the like. Advantageous efficiencies with respect, *inter alia*, to time and expense are thus obtained.

The TCR and Ig genes can generate millions of distinct proteins via somatic mutation. Because of this diversity-generating mechanism, the hypervariable complementarity determining regions of these genes can encode sequences that can interact with millions of ligands, and these regions are linked to a constant region that can transmit a signal to the cell indicating binding of the protein's cognate ligand. The adaptive immune system employs several strategies to generate a repertoire of T- and B-cell antigen receptors with sufficient diversity to recognize the universe of potential pathogens. In $\alpha\beta$ and $\gamma\delta$ T cells, which primarily recognize peptide antigens presented by MHC molecules, most of this receptor diversity is contained within the third complementarity-determining region (CDR3) of the T cell receptor (TCR) α and β chains (or γ and δ chains).

The assay technology uses two pools of primers to provide for a highly multiplexed PCR reaction. The first, "forward" pool (e.g., by way of illustration and not limitation, V-segment oligonucleotide primers described herein may in certain preferred embodiments be used as "forward" primers when J-segment oligonucleotide primers are used as "reverse" primers according to commonly used PCR terminology, but the skilled person will appreciate that in certain other embodiments J-segment primers may be regarded as "forward" primers when used with V-segment "reverse" primers) includes an oligonucleotide primer that is specific to (e.g., having a nucleotide sequence complementary to a unique sequence region of) each V-region encoding segment ("V segment") in the respective TCR or Ig gene locus. In certain embodiments, primers targeting a highly conserved region are used, to simultaneously capture many V segments, thereby reducing the number of primers required in the multiplex PCR. Similarly, in certain embodiments, the "reverse" pool primers anneal to a conserved sequence in the joining ("J") segment.

Each primer may be designed so that a respective amplified DNA segment is obtained that includes a sequence portion of sufficient length to identify each J segment unambiguously based on sequence differences amongst known J-region encoding gene segments in the human genome database, and also to include a sequence portion to which a J-segment-specific primer may anneal for resequencing. This design of V- and J-segment-specific primers enables direct observation of a large fraction of the somatic rearrangements present in

the adaptive immune receptor gene repertoire within an individual. This feature in turn enables rapid comparison of the TCR and/or Ig repertoires (i) in individuals having a particular disease, disorder, condition or other indication of interest (e.g., cancer, an autoimmune disease, an inflammatory disorder or other condition) with (ii) the TCR and/or Ig repertoires of control subjects who are free of such diseases, disorders conditions or indications.

The term "gene" means the segment of DNA involved in producing a polypeptide chain such as all or a portion of a TCR or Ig polypeptide (e.g., a CDR3-containing polypeptide); it includes regions preceding and following the coding region "leader and trailer" as well as intervening sequences (introns) between individual coding segments (exons), and may also include regulatory elements (e.g., promoters, enhancers, repressor binding sites and the like), and may also include recombination signal sequences (RSSs) as described herein.

The nucleic acids of the present embodiments, also referred to herein as polynucleotides, and including oligonucleotides, may be in the form of RNA or in the form of DNA, which DNA includes cDNA, genomic DNA, and synthetic DNA. The DNA may be double-stranded or single-stranded, and if single stranded may be the coding strand or non-coding (anti-sense) strand. A coding sequence which encodes a TCR or an immunoglobulin or a region thereof (e.g., a V region, a D segment, a J region, a C region, etc.) for use according to the present embodiments may be identical to the coding sequence known in the art for any given TCR or immunoglobulin gene regions or polypeptide domains (e.g., V-region domains, CDR3 domains, etc.), or may be a different coding sequence, which, as a result of the redundancy or degeneracy of the genetic code, encodes the same TCR or immunoglobulin region or polypeptide.

In one embodiment, the present disclosure provides a plurality of V segment primers and a plurality of J segment primers, wherein the plurality of V segment primers and the plurality of J segment primers amplify substantially all combinations of the V and J segments of a rearranged immune receptor locus. By substantially all combinations is meant at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more of all the combinations of the V and J segments of a rearranged immune receptor locus. In certain embodiments, the plurality of V segment primers and the plurality of J segment primers amplify all of the combinations of the V and J segments of a rearranged immune receptor locus.

In general, a multiplex PCR system may use at least 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25, and in certain embodiments, at least 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, or 39, and in other embodiments 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 65, 70, 75, 80, 85, or more forward primers, in which each forward primer specifically hybridizes to or is complementary to a sequence corresponding to one or more V region segments. Illustrative V region primers for amplification of the TCR β are shown in SEQ ID NOS:1-52 (see also Table 1). Illustrative TCR γ V region primers are provided in SEQ ID NOS:546-549. Illustrative IgHV region primers are provided in SEQ ID NOS:550-633. V region gene segment sequences may thus be used to design V region primers. Exemplary TCRB V region gene segment sequences are set forth in the sequence listing at SEQ ID NOS:1-52, 66-201, 644-695, 709-839, and 843-879. Exemplary TCRG V region gene segment sequences are set forth in SEQ ID NOS:221-238 and 546-549. Exemplary IgH V region gene segment sequences are set forth in SEQ ID NOS:255-545 and 550-633.

TABLE 1

Table 1A. TCRB oligonucleotide sequences targeting the 52 TCRBV and 13 TCRBJ gene segments.

Primer Name	SEQ NO: ID	Sequence (5' to 3')
TRBV25-1	644	GGAGATCTTCCTCTGAGTCAACAGTCTCCAGAATA
TRBV12-1	645	GGATTGATTCTCAGCACAGATGCCTGATGT
TRBV12-5	646	GATTCTCAGCAGAGATGCCTGATGCAACTTTA
TRBV2	647	AAGTCCTGAAATATTCGATGATCAATTCTCAGTTGAAAGGCC
TRBV16	648	AGCTAAGTGCCTCCCAAATTCAACCCT
TRBV5-1	649	CGATTCTCAGGGCGCCAGTTCTCTA
TRBV14	650	TCTTAGCTGAAAGGACTGGAGGGACGTAT
TRBV12-4	651	GAGGATCGATTCTCAGCTAAGATGCCTAATGC
TRBV28	652	TCCTGAGGGTACAGTGTCTCTAGAGAGA
TRBV27	653	GATGTTCTGAAGGGTACAAAGTCTCTCGAAAAG
TRBV5-4	654	CTCCTAGATTCTCAGGTCTCCAGTCCCTA
TRBV7-1	655	CGTGATCGGTTCTCTGCACAGAGGT
TRBV19	656	GCTGAAGGGTACAGCGTCTCTCGGG
TRBV5-3	657	CGATTCTCAGGGCGCCAGTTCCATG
TRBV9	658	CAACAGTCCCTGACTTGCACACTCTGAACAAAC
TRBV6-7	659	AGAAGTTCCAATGGCTACAATGTCTCCAGATC
TRBV6-4	660	AAGTCCCTGATGGTTATAGTGTCTCCAGAGC
TRBV6-1	661	GTCCCCAATGGCTACAATGTCTCCAGATT
TRBV7-9	662	TTCTCTGCAGAGAGGCCCTAAGGGATCT
TRBV7-3	663	GCCCAACGATCGGTTCTTGAGT
TRBV7-4	664	CCAGTGGTCGGTTCTGCAGAG
TRBV5-6	665	GCAACTCCCTGATCGATTCTCAGGTCA
TRBV5-8	666	CAGAGGAAACTTCCCTCTAGATTTTCAGGTG
TRBV7-8	667	GCCCAGTGATCGTTCTTGAGAAA
TRBV12-2	668	CGATTCTCAGCTGAGAGGCCCTGATGG
TRBV15	669	AGGCCGAACACTTCTTGCTTTCTGAC
TRBV6-2	670	CAAAGGAGAGGTCCCTGATGGCTACAA
TRBV23-1	671	GATTCTCATCTCAATGCCCAAGAACGC
TRBV10-2	672	CAGATAAAGGAGAAGTCCCCGATGGCTATGT
TRBV30	673	CAGGACCGGCAGTTCATCCTGAGT
TRBV10-3	674	AGATACTGACAAAGGAGAAGTCTCAGATGGCTATAG
TRBV6-6	675	GACAAAGGAGAAGTCCGAATGGCTACAAAC
TRBV13	676	CCCTGATCGATTCTCAGCTAACAGTTCACT
TRBV4-1	677	CCTGAATGCCCAACAGCTCTCTTAAAC

TABLE 1-continued

Table 1A. TCRB oligonucleotide sequences targeting the 52 TCRBV and 13 TCRBJ gene segments.

Primer Name	SEQ ID NO:	Sequence (5' to 3')
TRBV4-3	678	CCTGAATGCCCAACAGCTCTCACTTATTCTGAAATA
TRBV26	679	GGAGATGTCTCTGAGAGGTATCATGTTCTTGAAATA
TRBV6-8	680	TACAATGTCTCTAGATTAACACAGAGGATTCCCAC
TRBV3-2	681	TTCTCACCTGACTCTCCAGACAAAGCTCAT
TRBV11-2	682	CCTAAGGATCGATTTCTGCAGAGAGGCTC
TRBV2	683	CCTGAATGCCCTGACAGCTCTCGCTTATA
TRBV3-1	684	GCTTCACCTAAATCTCCAGACAAAGCTCACTTAAA
TRBV29-1	685	CATCAGCCGCCAACCTAACATTCTCAA
TRBV18	686	ATTTTCTGCTGAATTCCAAAGAGGCC
TRBV17	687	ATTCACAGCTGAAAGACCTAACGGAACGT
TRBV20-1	688	CAAGCCTGACCTTGTCCACTCTGACA
TRBV7-6	689	GGTTCTCTGCAGAGAGGCCCTGAGG
TRBV24-1	690	GAGAGATCTCTGATGGATACTGTCTCGACA
TRBV7-2	691	GATCGCTTCTCTGCAGAGAGGACTGG
TRBV6-9	692	AAGGAGAAGTCCCCGATGGCTACAATGTA
TRBV6-5	693	AAGGAGAAGTCCCCAATGGCTACAATGTC
TRBV5-5	694	AAGAGGAAACTTCCCTGATCGATTCTCAGC
TRBV10-1	695	GACACTAACAAAGGAGAAGTCTCAGATGGCTACAG
TRBJ1-1	696	TTACCTACAACTGTGAGTCGGTGCCTGTCCAAA
TRBJ1-2	697	TACAACGGTTAACCTGGTCCCCGAACCGAA
TRBJ1-3	698	ACCTACAAACAGTGAGCCAACCTCCCTCTCCAAAA
TRBJ1-4	699	CAAGACAGAGAGCTGGTTCCACTGCCAAAA
TRBJ1-5	700	ACCTAGGATGGAGAGTCGAGTCCCACACCAAA
TRBJ1-6	701	TCACAGTGAGCCTGGTCCCCTTCCAAA
TRBJ2-1	702	CGGTGAGCCGTGTCCTGGCCCGAA
TRBJ2-2	703	CCAGTACGGTCAGCCTAGAGCCTCTCCAAA
TRBJ2-3	704	ACTGTCAGCCGGTGCCTGGGCCAAA
TRBJ2-4	705	AGAGCCGGTCCGGCGCGAA
TRBJ2-5	706	GGAGCCCGTGCCTGGCCCGAA
TRBJ2-6	707	GTCAGCCTGCTGCCGGCCCCGAA
TRBJ2-7	708	G TGAGCCTGGTGCCCCGGCCGAA

TABLE 1B

List of TCRB RN2 oligonucleotide sequences targeting the 52
TCRBV and 13 TCRBJ gene segments.

Primer Name	SEQ ID NO: Sequence
TRBV25-1_RN2v3	1 GGAGATCTTCCTCTGAGTCAACAGTCTCCAGAATArAGGAC/3SpC3/
TRBV12-1_RN2v3	2 GGATTGATTCTCAGCACAGATGCCTGATGTrATCAT/3SpC3/
TRBV12-5_RN2v3	3 GATTCTCAGCAGAGATGCCTGATGCAACTTArGCCAC/3SpC3/
TRBV2_RN2v3	4 AAGTCTGAAATATTGATGATCAATTCTCAGTTGAAAGGCCrUGATG/3SpC3/
TRBV16_RN2v3	5 AGCTAAGTGCTCCCAAATTCACCCTrGTAGC/3SpC3/
TRBV5-1_RN2v3	6 CGATTCTCAGGGGCCAGTTCTArACTCT/3SpC3/
TRBV14_RN2v3	7 TCTTAGCTGAAAGGACTGGAGGGACGTArUCTAC/3SpC3/
TRBV12-4_RN2v3	8 GAGGATCGATTCTCAGCTAACATGCCTAArATCAT/3SpC3/
TRBV28_RN2v3	9 TCCTGAGGGGTACAGTGTCTAGAGAGArAGAAG/3SpC3/
TRBV27_RN2v3	10 GATGTTCCCTGAAGGGTACAAAGTCTCTGAAAAGrAGAAG/3SpC3/
TRBV5-4_RN2v3	11 CTCCTAGATTCTCAGGTCTCAGTTCCCTArATTAT/3SpC3/
TRBV7-1_RN2v3	12 CGTGATCGGTTCTGCACAGAGGTrCTGAG/3SpC3/
TRBV19_RN2v3	13 GCTGAAGGGTACAGCGTCTCAGGGrAGAAG/3SpC3/
TRBV5-3_RN2v3	14 CGATTCTCAGGGGCCAGTTCCATGrACTGT/3SpC3/
TRBV9_RN2v3	15 CAACAGTCCCTGACTGCACTCTGAACAArCTGAG/3SpC3/
TRBV6-7_RN2v3	16 AGAAAGTCCAATGGCTACAATGTCCTCAGATCrAAACA/3SpC3/
TRBV6-4_RN2v3	17 AAGTCCCTGATGGTTAGTGTCTCAGAGCGrAAACA/3SpC3/
TRBV6-1_RN2v3	18 GTCCCCAATGGCTACAATGTCCTCAGATrAAACA/3SpC3/
TRBV7-9_RN2v3	19 TTCTCTGCAGAGAGGCCTAAGGGATCTCTC/3SpC3/
TRBV7-3_RN2v3	20 GCCCAACGATCGGTTCTTGCArCAGGC/3SpC3/
TRBV7-4_RN2v3	21 CCAGTGGTCGGTTCTCTGCAGAGrAGGCC/3SpC3/
TRBV5-6_RN2v3	22 GCAACTCCCTGATCGATTCTCAGGTCArCCAGT/3SpC3/
TRBV5-8_RN2v3	23 CAGAGGAAACTCCCTCTAGATTTCAAGGTCGrCCAGT/3SpC3/
TRBV7-8_RN2v3	24 GCCCAGTGATCGCTCTTGCArGGCCT/3SpC3/
TRBV12-2_RN2v3	25 CGATTCTCAGCTGAGAGGCCGATGGrATCAT/3SpC3/
TRBV15_RN2v3	26 AGGCCGAACACTTCTTCTGCTTCTGACrATCCG/3SpC3/
TRBV6-2_RN2v3	27 CAAAGGAGAGTCCTGATGGCTACAArUGTCT/3SpC3/
TRBV23-1_RN2v3	28 GATTCTCATCTCATGCCCAAGAACGCrACCCT/3SpC3/
TRBV10-2_RN2v3	29 CAGATAAAAGGAGAAGTCCCCGATGGCTATGTrUGTCT/3SpC3/
TRBV30_RN2v3	30 CAGGACCGGCAGTTCATCCTGAGTrUCTAA/3SpC3/
TRBV10-3_RN2v3	31 AGATACTGACAAAGGAGAAGTCTCAGATGGCTATAGrUGTCT/3SpC3/
TRBV6-6_RN2v3	32 GACAAAGGAGAAGTCCCGAATGGCTACAArGTCTC/3SpC3/
TRBV13_RN2v3	33 CCCTGATCGATTCTCAGCTCAACAGTTCArGACTA/3SpC3/
TRBV4-1_RN2v3	34 CCTGAATGCCCAACAGCTCTCTTAArCTTCA/3SpC3/
TRBV4-3_RN2v3	35 CCTGAATGCCCAACAGCTCTCACTTATTCrCTTCA/3SpC3/
TRBV26_RN2v3	36 GGAGATGTCCTGAGAGGTATCATGTTCTGAAATArCTATA/3SpC3/
TRBV6-8_RN2v3	37 TACAATGTCCTAGATTAAACACAGAGGATTCCCACrUCAGG/3SpC3/

TABLE 1B-continued

List of TCRB RN2 oligonucleotide sequences targeting the 52
TCRBV and 13 TCRBJ gene segments.

Primer Name	SEQ ID NO: Sequence
TRBV3_2_RN2v3	38 TTCTCACCTGACTCTCCAGACAAAGCTCATrUTAAA/3SpC3/
TRBV11_2_RN2v3	39 CCTAAGGATCGATTCTGCAGAGAGGCTrAAAGG/3SpC3/
TRBV2_RN2v3	40 CCTGAATGCCCTGACAGCTCTCGCTTATArCCTTC/3SpC3/
TRBV3_1_RN2v3	41 GCTTCTCACCTAAATCTCCAGACAAAGCTCACTAAArUCTTC/3SpC3/
TRBV29_1_RN2v3	42 CATCAGCCGCCAACCTAACATTCTCAArCTCTG/3SpC3/
TRBV18_RN2v3	43 ATTTCTGCTGAATTCCCAAAGAGGGCCrCCAGC/3SpC3/
TRBV17_RN2v3	44 ATTACACAGCTGAAAGACCTAACGGAACGTrCTTCC/3SpC3/
TRBV20_1_RN2v3	45 CAAGCCTGACCTTGTCACACTCTGACArGTGAC/3SpC3/
TRBV7_6_RN2v3	46 GGTCTCTGAGAGAGGCCCTGAGGrGATCC/3SpC3/
TRBV24_1_RN2v3	47 GAGAGATCTCTGATGGATACTGTCTCTGACArGGCAC/3SpC3/
TRBV7_2_RN2v3	48 GATCGCTCTCTGCAGAGAGGACTGGrGGGAT/3SpC3/
TRBV6_9_RN2v3	49 AAGGAGAAAGTCCCCATGGCTACAATGTArUCCAG/3SpC3/
TRBV6_5_RN2v3	50 AAGGAGAAAGTCCCAATGGCTACAATGTCrUCCAG/3SpC3/
TRBV5_5_RN2v3	51 AAGGAGAAACTCCCTGATCGATTCTCAGCrUCGCC/3SpC3/
TRBV10_1_RN2v3	52 GACACTAACAAAGGAGAAGTCTCAGATGGCTACAGrUGTCT/3SpC3/
TRBJ1_1_RN2v3	53 TTACCTACAACTGTGAGTCTGGTCCTTGTCCAArGAAAG/3SpC3/
TRBJ1_2_RN2v3	54 TACAAACGGTTAACCTGGTCCCCGAAACCGAArGGTGT/3SpC3/
TRBJ1_3_RN2v3	55 ACCTACAAACAGTGAGCCAATTCCCTCTCCAAAArUATAT/3SpC3/
TRBJ1_4_RN2v3	56 CAAGACAGAGAGCTGGTTCCACTGCCAAAArAACAG/3SpC3/
TRBJ1_5_RN2v3	57 ACCTAGGATGGAGAGTCGAGTCCCACCAAArATGCT/3SpC3/
TRBJ1_6_RN2v3	58 TCACAGTGAGCCTGGTCCGTCCAAAArGTGGA/3SpC3/
TRBJ2_1_RN2v3	59 CGGTGAGCCGTGTCCTGGCCCGAArGAAC/3SpC3/
TRBJ2_2_RN2v3	60 CCAGTACGGTCAGCCTAGAGCCTCTCCAAAArAAACA/3SpC3/
TRBJ2_3_RN2v3	61 ACTGTCAGCCGGTGCCTGGGCCAAAArATACT/3SpC3/
TRBJ2_4_RN2v3	62 AGAGCCGGTCCCCCGCCGAArGTACT/3SpC3/
TRBJ2_5_RN2v3	63 GGAGCCGCGTGCCTGGCCCGAArGTACT/3SpC3/
TRBJ2_6_RN2v3	64 GTCAGCCTGCTGCCGGCCCGAArAGTCA/3SpC3/
TRBJ2_7_RN2v3	65 GTGAGCCTGGTGCCGGCCCGAArGTACT/3SpC3/

In the RN2 oligonucleotides of Table 1B, “r” represents a ribonucleotide base in the oligonucleotide sequence and “/3SpC3/” represents a 3' three-carbon spacer on the hydroxyl group, preventing polymerase extension and amplification. The DNA repair endonuclease cleaves the oligonucleotide at the ribonucleotide after hybridization to a complementary sequence, creating an unblocked hydroxyl group that can be extended by a polymerase.

The multiplex PCR system also uses at least 3, 4, 5, 6, or 7, and in certain embodiments, 8, 9, 10, 11, 12 or 13 reverse primers, in which each reverse primer specifically hybridizes to or is complementary to a sequence corresponding to one or

⁵⁵ more J region segments. Illustrative TCR β J segment primers are provided in SEQ ID NOs:53-65 (see also Table 1). Illustrative TCR γ J segment primers are provided in SEQ ID NOs:634-637. Illustrative IgH J segment primers are provided in SEQ ID NOs:638-643. J region gene segment sequences may thus be used to design J region primers. Exemplary TCRB J region segment sequences are set forth in SEQ ID NOS:53-65, 202-214, 696-708, and 880-883. Exemplary TCRG J region gene segment sequences are set forth in SEQ ID NOS:215-220 and 634-637. Exemplary IgH J region gene segment sequences are set forth in SEQ ID NOS:239-254 and 638-643. In one embodiment, there is a J segment primer for every J segment.

35

Oligonucleotides or polynucleotides that are capable of specifically hybridizing or annealing to a target nucleic acid sequence by nucleotide base complementarity may do so under moderate to high stringency conditions. For purposes of illustration, suitable moderate to high stringency conditions for specific PCR amplification of a target nucleic acid sequence would be between 25 and 80 PCR cycles, with each cycle consisting of a denaturation step (e.g., about 10-30 seconds (s) at at least about 95° C.), an annealing step (e.g., about 10-30 s at about 60-68° C.), and an extension step (e.g., about 10-60 s at about 60-72° C.), optionally according to certain embodiments with the annealing and extension steps being combined to provide a two-step PCR. As would be recognized by the skilled person, other PCR reagents may be added or changed in the PCR reaction to increase specificity of primer annealing and amplification, such as altering the magnesium concentration, optionally adding DMSO, and/or the use of blocked primers, modified nucleotides, peptide-nucleic acids, and the like.

In certain embodiments, nucleic acid hybridization techniques may be used to assess hybridization specificity of the primers described herein. Hybridization techniques are well known in the art of molecular biology. For purposes of illustration, suitable moderately stringent conditions for testing the hybridization of a polynucleotide as provided herein with other polynucleotides include prewashing in a solution of 5×SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0); hybridizing at 50° C.-60° C., 5×SSC, overnight; followed by washing twice at 65° C. for 20 minutes with each of 2×, 0.5× and 0.2×SSC containing 0.1% SDS. One skilled in the art will understand that the stringency of hybridization can be readily manipulated, such as by altering the salt content of the hybridization solution and/or the temperature at which the hybridization is performed. For example, in another embodiment, suitable highly stringent hybridization conditions include those described above, with the exception that the temperature of hybridization is increased, e.g., to 60° C.-65° C. or 65° C.-70° C.

In certain embodiments, the primers are designed not to cross an intron/exon boundary. The forward primers in certain embodiments anneal to the V segments in a region of relatively strong sequence conservation between V segments so as to maximize the conservation of sequence among these primers. Accordingly, this minimizes the potential for differential annealing properties of each primer, and so that the amplified region between V and J primers contains sufficient TCR or Ig V sequence information to identify the specific V gene segment used. In one embodiment, the J segment primers hybridize with a conserved element of the J segment, and have similar annealing strength. In one particular embodiment, the J segment primers anneal to the same conserved framework region motif.

Oligonucleotides (e.g., primers) can be prepared by any suitable method, including direct chemical synthesis by a method such as the phosphotriester method of Narang et al., 1979, *Meth. Enzymol.* 68:90-99; the phosphodiester method of Brown et al., 1979, *Meth. Enzymol.* 68:109-151; the diethylphosphoramidite method of Beaucage et al., 1981, *Tetrahedron Lett.* 22:1859-1862; and the solid support method of U.S. Pat. No. 4,458,066, each incorporated herein by reference. A review of synthesis methods of conjugates of oligonucleotides and modified nucleotides is provided in Goodchild, 1990, *Bioconjugate Chemistry* 1(3): 165-187, incorporated herein by reference.

The term "primer," as used herein, refers to an oligonucleotide capable of acting as a point of initiation of DNA synthesis under suitable conditions. Such conditions include

36

those in which synthesis of a primer extension product complementary to a nucleic acid strand is induced in the presence of four different nucleoside triphosphates and an agent for extension (e.g., a DNA polymerase or reverse transcriptase) in an appropriate buffer and at a suitable temperature.

A primer is preferably a single-stranded DNA. The appropriate length of a primer depends on the intended use of the primer but typically ranges from 6 to 50 nucleotides, or in certain embodiments, from 15-35 nucleotides. Short primer molecules generally require cooler temperatures to form sufficiently stable hybrid complexes with the template. A primer need not reflect the exact sequence of the template nucleic acid, but must be sufficiently complementary to hybridize with the template. The design of suitable primers for the amplification of a given target sequence is well known in the art and described in the literature cited herein.

As described herein, primers can incorporate additional features which allow for the detection or immobilization of the primer but do not alter the basic property of the primer, that of acting as a point of initiation of DNA synthesis. For example, primers may contain an additional nucleic acid sequence at the 5' end which does not hybridize to the target nucleic acid, but which facilitates cloning, detection, or sequencing of the amplified product. The region of the primer which is sufficiently complementary to the template to hybridize is referred to herein as the hybridizing region.

As used herein, a primer is "specific," for a target sequence if, when used in an amplification reaction under sufficiently stringent conditions, the primer hybridizes primarily to the target nucleic acid. Typically, a primer is specific for a target sequence if the primer-target duplex stability is greater than the stability of a duplex formed between the primer and any other sequence found in the sample. One of skill in the art will recognize that various factors, such as salt conditions as well as base composition of the primer and the location of the mismatches, will affect the specificity of the primer, and that routine experimental confirmation of the primer specificity will be needed in many cases. Hybridization conditions can be chosen under which the primer can form stable duplexes only with a target sequence. Thus, the use of target-specific primers under suitably stringent amplification conditions enables the selective amplification of those target sequences which contain the target primer binding sites.

In particular embodiments, primers for use in the methods described herein comprise or consist of a nucleic acid of at least about 15 nucleotides long that has the same sequence as, or is complementary to, a 15 nucleotide long contiguous sequence of the target V or J segment. Longer primers, e.g., those of about 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 45, or 50 nucleotides long that have the same sequence as, or sequence complementary to, a contiguous sequence of the target V or J segment that is at least 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 45, or 50 nucleotides long, will also be of use in certain embodiments. All intermediate lengths of the aforementioned primers are contemplated for use herein. As would be recognized by the skilled person, the primers may have additional sequence added (e.g., nucleotides that may not be the same as or complementary to the target V or J segment), such as restriction enzyme recognition sites, adaptor sequences for sequencing, bar code sequences, and the like (see e.g., primer sequences provided herein and in the sequence listing). Therefore, the length of the primers may be longer, such as 55, 56, 57, 58, 59, 60, 65, 70, 75, nucleotides in length or more, depending on the specific use or need. For example, in

one embodiment, the forward and reverse primers are both modified at the 5' end with the universal forward primer sequence compatible with a DNA sequencer.

Also contemplated for use in certain embodiments are adaptive immune receptor V-segment or J-segment oligonucleotide primer variants that may share a high degree of sequence identity to the oligonucleotide primers for which nucleotide sequences are presented herein, including those set forth in the Sequence Listing or portions thereof that are at least 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 45, or 50 nucleotides long. Thus, in these and related embodiments, adaptive immune receptor V-segment or J-segment oligonucleotide primer variants may have substantial identity to the adaptive immune receptor V-segment or J-segment oligonucleotide primer sequences disclosed herein, for example, such oligonucleotide primer variants may comprise at least 70% sequence identity, preferably at least 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% or higher sequence identity compared to a reference polynucleotide sequence such as the oligonucleotide primer sequences disclosed herein, using the methods described herein (e.g., BLAST analysis using standard parameters). One skilled in this art will recognize that these values can be appropriately adjusted to determine corresponding ability of an oligonucleotide primer variant to anneal to an adaptive immune receptor segment-encoding polynucleotide by taking into account codon degeneracy, reading frame positioning and the like. Typically, oligonucleotide primer variants will contain one or more substitutions, additions, deletions and/or insertions, preferably such that the annealing ability of the variant oligonucleotide is not substantially diminished relative to that of an adaptive immune receptor V-segment or J-segment oligonucleotide primer sequence that is specifically set forth herein. As also noted elsewhere herein, in preferred embodiments adaptive immune receptor V-segment and J-segment oligonucleotide primers are designed to be capable of amplifying a rearranged TCR or IGH sequence that includes the coding region for CDR3.

According to certain embodiments contemplated herein, the primers for use in the multiplex PCR methods of the present disclosure may be functionally blocked to prevent non-specific priming of non-T or B cell sequences. For example, the primers may be blocked with chemical modifications as described in U.S. patent application publication US2010/0167353. According to certain herein disclosed embodiments, the use of such blocked primers in the present multiplex PCR reactions involves primers that may have an inactive configuration wherein DNA replication (i.e., primer extension) is blocked, and an activated configuration wherein DNA replication proceeds. The inactive configuration of the primer is present when the primer is either single-stranded, or when the primer is specifically hybridized to the target DNA sequence of interest but primer extension remains blocked by a chemical moiety that is linked at or near to the 3' end of the primer.

The activated configuration of the primer is present when the primer is hybridized to the target nucleic acid sequence of interest and is subsequently acted upon by RNase H or another cleaving agent to remove the 3' blocking group, thereby allowing an enzyme (e.g., a DNA polymerase) to catalyze primer extension in an amplification reaction. Without wishing to be bound by theory, it is believed that the kinetics of the hybridization of such primers are akin to a second order reaction, and are therefore a function of the T cell or B cell gene sequence concentration in the mixture. Blocked primers minimize non-specific reactions by requir-

ing hybridization to the target followed by cleavage before primer extension can proceed. If a primer hybridizes incorrectly to a sequence that is related to the desired target sequence but which differs by having one or more non-complementary nucleotides that result in base-pairing mismatches, cleavage of the primer is inhibited, especially when there is a mismatch that lies at or near the cleavage site. This strategy to improve the fidelity of amplification reduces the frequency of false priming at such locations, and thereby increases the specificity of the reaction. As would be recognized by the skilled person, reaction conditions, particularly the concentration of RNase H and the time allowed for hybridization and extension in each cycle, can be optimized to maximize the difference in cleavage efficiencies between highly efficient cleavage of the primer when it is correctly hybridized to its true target sequence, and poor cleavage of the primer when there is a mismatch between the primer and the template sequence to which it may be incompletely annealed.

As described in US2010/0167353, a number of blocking groups are known in the art that can be placed at or near the 3' end of the oligonucleotide (e.g., a primer) to prevent extension. A primer or other oligonucleotide may be modified at the 3'-terminal nucleotide to prevent or inhibit initiation of DNA synthesis by, for example, the addition of a 3' deoxyribonucleotide residue (e.g., cordycepin), a 2',3'-dideoxyribonucleotide residue, non-nucleotide linkages or alkane-diol modifications (U.S. Pat. No. 5,554,516). Alkane diol modifications which can be used to inhibit or block primer extension have also been described by Wilk et al., (1990 *Nucleic Acids Res.* 18 (8):2065), and by Arnold et al. (U.S. Pat. No. 6,031,091). Additional examples of suitable blocking groups include 3' hydroxyl substitutions (e.g., 3'-phosphate, 3'-triphosphate or 3'-phosphate diesters with alcohols such as 3-hydroxypropyl), 2',3'-cyclic phosphate, 2' hydroxyl substitutions of a terminal RNA base (e.g., phosphate or sterically bulky groups such as triisopropyl silyl (TIPS) or tert-butyl dimethyl silyl (TBDMS)). 2'-alkyl silyl groups such as TIPS and TBDMS substituted at the 3'-end of an oligonucleotide are described by Laikhter et al., U.S. patent application Ser. No. 11/686,894, which is incorporated herein by reference. Bulky substituents can also be incorporated on the base of the 3'-terminal residue of the oligonucleotide to block primer extension.

In certain embodiments, the oligonucleotide may comprise a cleavage domain that is located upstream (e.g., 5' to) of the blocking group used to inhibit primer extension. As examples, the cleavage domain may be an RNase H cleavage domain, or the cleavage domain may be an RNase H2 cleavage domain comprising a single RNA residue, or the oligonucleotide may comprise replacement of the RNA base with one or more alternative nucleosides. Additional illustrative cleavage domains are described in US2010/0167353. Oligonucleotide primers that comprise an RNase H2 cleavage domain upstream to a blocking group that inhibits primer extension are referred to as "RN2 modified" primers. Exemplary RN2 modified primers are listed above in Table 1B. Thus, a multiplex PCR system may use 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, or more forward primers, wherein each forward primer is complementary to a single functional TCR or Ig V segment or a small family of functional TCR or Ig V segments, e.g., a TCR V β segment, or (see e.g., the TCR primers as shown in Table 1), and, for example, thirteen reverse primers, each specific to a TCR or Ig J segment, such as TCR J β segment (see e.g., Table 1). In another embodiment, a multiplex PCR reaction may use four forward primers each specific to one or more functional TCR γ V segment and

four reverse primers each specific for one or more TCR γ J segments. In another embodiment, a multiplex PCR reaction may use 84 forward primers each specific to one or more functional V segments and six reverse primers each specific for one or more J segments.

The present methods provide the ability to quantify the relative number of T or B cells in a complex mixture of cells by determining the relative representation of adaptive immune cell DNA in a DNA sample extracted from the cell mixture, by multiplex PCR using real-time quantitative PCR methods. Real-time PCR is a technique that evaluates the level of PCR product accumulation during successive amplification cycles (see e.g., Gibson *et al.*, *Genomic Research* 6:995-1001, 1990; Heid *et al.*, *Genome Research* 6:986-904, 1996, *Real-Time PCR: Current Technology and Applications*, Edited by Julie Logan, Kirstin Edwards and Nick Saunders, 2009, Caister Academic Press, Norfolk, UK). This technique permits quantitative evaluation of DNA (or mRNA/cDNA) levels in multiple samples. Briefly, DNA (or mRNA/cDNA) is extracted from a sample (e.g., tumor and normal tissue) using standard techniques. Real-time PCR is performed using the multiplex PCR primer sets as described herein using, for example, any of a variety of commercially available real-time PCR machines, such as LIGHTCYCLER®480 System (Roche Diagnostics Corporation, Indianapolis, IN), real-time detection systems from Bio-Rad (e.g., CFX384™ or other similar systems; Bio-Rad; Hercules, CA), or the ECO™ real-time PCR system (Illumina Inc., San Diego CA).

A number of established qPCR methodologies are described herein and may be employed according to certain preferred embodiments of the present invention, but the invention is not intended to be so limited and also contemplates digital PCR (dPCR, e.g., droplet digital PCR or “ddPCR”) and various quantitative PCR techniques and instrumentation, including by way of illustration and not limitation the ABI QUANTSTUDIO™12K Flex System (Life Technologies, Carlsbad, Calif.), the QUANTALIFE™digital PCR system (BioRad, Hercules, Calif.) and the RAINDANCE™microdroplet digital PCR system (Rain-Dance Technologies, Lexington, MA) (e.g., Pekin *et al.*, 2011 *Lab. Chip* 11(13):2156; Zhong *et al.*, 2011 *Lab. Chip* 11(13): 2167; Tewhey *et al.*, 2009 *Nature Biotechnol.* 27:1025; 2010 *Nature Biotechnol.* 28:178), any of which may be adapted by the skilled person for use with the herein described compositions and methods.

Quantification of amplified DNA molecules that are the products of qPCR or dPCR or other quantitative PCR techniques may be achieved by detecting a level of a DNA-quantifying signal that is generated by a detectable indicator of the presence of DNA. In preferred embodiments, the detectable indicator generates a DNA-quantifying signal that is a fluorescent signal, using well known reagents and detection instrumentation. In one exemplary embodiment, amplified PCR product may be detected using a DNA intercalating dye, such as SYBR™ green, a fluorescent dye that only intercalates into double-stranded DNA, i.e., the DNA-quantifying signal is SYBR™ green fluorescence and the detectable indicator is SYBR™ green, such that fluorimetric quantification of the fluorescent signal provides measureable DNA-quantifying signal level. Other illustrative dyes that may be used as detectable indicators to generate measureable levels of DNA-quantifying signals include SYTO9, SYTO-82 and SYTO-13 EVAGREEN™ (see e.g., Anal. Biochem., 340:24-34, 2005; *Nucleic Acid Res.* 35: e127, 2007). These detectable indicators may advantageously permit quantitative determination of PCR products without the use of sequence-specific oligonucleotide probes, such as oligonucleotide probes for use in

real-time qPCR that may bear a detectable labeling moiety such as a fluorescent moiety and/or a fluorescence quencher or dequenching moiety, examples of which are described below.

5 The increase in fluorescence may be monitored at one or a plurality of timepoints during the amplification process, including monitoring fluorescence throughout all or substantially all of the amplification process. A threshold for detection of fluorescence above background is determined, 10 where the cycle threshold, C_t , is the cycle (i.e., the cycle number in the succession of PCR cycles, where each cycle comprises steps of DNA denaturation, primer annealing, and template-directed DNA synthesis via primer extension) at which the fluorescence crosses the threshold. During the 15 exponential phase, the quantity of DNA theoretically doubles every cycle. Therefore, relative amounts of DNA can be calculated, e.g., a first sample for which the C_{t_1} is three cycles earlier than the C_{t_2} of a second sample has $2^3=8$ times more template than the second sample.

20 The amount of DNA or RNA in the test sample is determined by comparing the real-time PCR results to a standard curve. The standard curve is generated for each qPCR run using a standard control DNA containing the gene or genes of interest. In one embodiment of the present disclosure, the 25 standard control is prepared by purifying DNA from adaptive immune cells, such as from T and/or B cells (e.g., from T cells or B cells bead sorted from peripheral blood). The purified DNA is quantified and then serially diluted to concentrations ranging from 60 picograms to 250 nanograms per reaction. The skilled person would understand that other similar standard control templates may also be used, such as plasmid DNA containing the target template(s) of interest.

In addition, in certain embodiments, an additional qPCR standard curve may be generated for amplification products 35 of all or a portion of an internal control gene that, unlike the rearranged TCR or Ig CDR3-encoding gene regions found in adaptive immune cells, is common to all of the cells in the test biological sample, i.e., in the adaptive immune cells and in the cells that are not adaptive immune cells. Non-limiting 40 examples of such internal control genes include those that encode β -actin, RNaseP, glyceraldehyde-3-phosphate dehydrogenase, MHC I (major histocompatibility complex type I antigens, such as HLA-A or HLA-B), cyclophilin, and others as are known in the art, and which may be amplified using appropriate concentrations of target DNA (or cDNA) as template. These and related embodiments permit standardization 45 of the initial DNA or RNA content of a tissue sample, and hence quantification of the total number of cells present in a test sample that comprises a mixture of cells (e.g., adaptive immune cells and other cells), based on the amount of internal control gene (e.g., β -actin and RNaseP) DNA that is detectable in qPCR, for comparison purposes.

Thus, the mean copy number for each test biological 55 sample in which rearranged adaptive immune receptor (TCR or Ig) encoding DNA is quantified as a measure of adaptive immune cells, may be normalized relative to the DNA quantity that is determined for the internal control gene, which is present at constant levels in adaptive immune cells and in cells that are not adaptive immune cells. For instance, determination of the amount of β -actin encoding DNA, or another appropriate internal control gene, permits evaluation of the level of adaptive immune receptor encoding DNA relative to the level of the internal control gene DNA in each test sample.

Accordingly, certain of the herein described methods for 60 quantifying the number of adaptive immune cells in a test sample that comprises a mixture of cells may further comprise quantifying the number of cells in the mixture of cells,

by amplifying test sample template DNA extracted from the test biological sample with a set of control primers, wherein the set of control primers amplifies an internal control gene DNA segment that is not specific to adaptive immune cells, to produce internal control gene amplification products. Concurrently with the amplification of the internal control gene segment, at one or a plurality of time points a DNA signal level is measured that is detectable for the internal control gene amplification products. This internal control gene amplification signal is compared, at the one or plurality of time points (e.g., in real time), to a reference DNA signal level that is detectable in amplification products of a known amount of the internal control gene DNA that has been amplified by the control primers, to provide a calibration standard for use as a reference. By this comparison, the amount of internal control gene DNA that is present in the test sample template DNA that was extracted from the test biological sample, can be quantified, from which the number of cells in the mixture of cells in the test sample can be determined. In certain such embodiments, the control primers are present in the same qPCR reaction as the reaction in which rearranged adaptive immune receptor encoding DNA is amplified with V-segment and J-segment primers. In certain other embodiments, the control primers are present in a separate qPCR reaction from the reaction in which amplification occurs using the V-segment and J-segment primers.

In another embodiment, matching primers and fluorescent probes (e.g., Taqman® probes from Roche Molecular Systems, Pleasanton, Calif.; or Molecular Probes® fluorescent dyes from Invitrogen Corp., Carlsbad, Calif.), 3' minor groove binding (MGB) DNA probes (e.g., dihydrocyclopyrrolindole tripeptides described by Kutyavin et al., 2000 *Nucl. Ac. Res.* 28:655-661), or other appropriate molecular beacons (see, e.g., Manganelli et al., 2001 *Meth. Mol. Med.* 54:295; Tyagi et al., 2000 *Nat. Biotech.* 18:1191) may be designed for genes of interest (e.g., TCR or Ig V and J segment genes; internal control genes) as described herein. Optimal concentrations of primers and probes may be initially determined by those of ordinary skill in the art, and control (e.g., β-actin) primers and probes may be obtained commercially from, for example, Perkin Elmer/Applied Biosystems (Foster City, Calif.). Table 2A shows exemplary probes designed to target the human TCRB gene family, using the PCR primers presented in Table 1A, the fluorophore FAM (6-carboxyfluorescein), the (MGB) minor groove-binder modification to increase Tm, and a non-fluorescent quencher (NFQ; e.g., QSY21, Kabelac et al., 2010 *Phys Chem Chem Phys* 12:9677; QSY9, Anderson et al., 2009 *Biochem.* 48:8516; 4-(4'-dimethylaminophenylazo)benzoic acid (DABCYL), Manganelli et al., 2001 *Meth. Mol. Med.* 54:295; BHQ-1, (4-(2-nitro-4-toluyldiazo)-2'-methoxy-5-methylazobenzene-4''-(N-ethyl)-N-ethyl-2-cyanoethyl-(N,N-diisopropyl)-phosphoramidite) or other members of the BHQ® series, available from Biosearch Technologies, Inc., Novato, Calif.). Related embodiments contemplate alternative means for generating high Tm probes in which the MGB is replaced, such as using longer probes without MGB, or using locked nucleic acids (LNA, see, e.g., Kaur et al., 2007 *Chem. Rev.* 107:4672). Alternative quenchers may also be employed, including fluorescent quenchers (e.g., Marras, 2006 *Meths. Mol. Biol.* 335:3; Stefflova et al., 2007 *Curr. Med. Chem.* 14:2110). Alternative fluorophores including TET, VIC, ROX, TAMRA, Cy3, Cy5, Hex, Yellow 555 and others may also be substituted for FAM (e.g., Marras, 2006; see also Molecular Probes® fluorescent dyes from Invitrogen Corp.,

Carlsbad, Calif.). Mixtures of fluorophores may also be used in certain embodiments, for example, to detect multiple V segments in a single reaction.

TABLE 2A

TaqMan® MGB probes for use with the PCR primers of Table 1A.			
	Gene segment	SEQ ID NO:	probe
10	TCRBV01p	709	FAM-ACTGCAGCAAGAAGACTCAGCT-MGB-NFQ
15	TCRBV02	710	FAM-AAGATCCGGTCCACAAAGCT-MGB-NFQ
15	TCRBV03-1	711	FAM-AATTCCCTGGAGCTTGGTACT-MGB-NFQ
15	TCRBV03-2p	712	FAM-AATTCCCTGGAGCTTGGTACT-MGB-NFQ
20	TCRBV04-1	713	FAM-CAGAACACTAGCCCTGTATCT-MGB-NFQ
20	TCRBV04-2	714	FAM-AGAAGACTCGGCCCTGTATCT-MGB-NFQ
20	TCRBV04-3	715	FAM-AGAAGACTCGGCCCTGTATCT-MGB-NFQ
25	TCRBV05-1	716	FAM-AATGTGAGCACCTTGGAGCT-MGB-NFQ
25	TCRBV05-2p	717	FAM-ACTGAGTCAAACACGGAGCT-MGB-NFQ
25	TCRBV05-3	718	FAM-AATGTGAGTCGCCTTGGAGCT-MGB-NFQ
30	TCRBV05-4	719	FAM-AATGTGAACGCCTTGGAGCT-MGB-NFQ
30	TCRBV05-5	720	FAM-TGTGAACGCCTTGGAGCT-MGB-NFQ
30	TCRBV05-6	721	FAM-TGTGAACGCCTTGGAGCT-MGB-NFQ
35	TCRBV05-7	722	FAM-TGTGAACGCCTTGGAGCT-MGB-NFQ
35	TCRBV05-8	723	FAM-TGTGAACGCCTTGGAGCT-MGB-NFQ
35	TCRBV06-1	724	FAM-CCTCCCAGACATCTGTACTT-MGB-NFQ
40	TCRBV06-2	725	FAM-TCCCTCCAAACATCTGTGT-MGB-NFQ
40	TCRBV06-3	726	FAM-TCCCTCCAAACATCTGTGT-MGB-NFQ
40	TCRBV06-4	727	FAM-TGCTGTACCCCTCAGACATCT-MGB-NFQ
45	TCRBV06-5	728	FAM-CCTCCCAGACATCTGTGTACTT-MGB-NFQ
45	TCRBV06-6	729	FAM-CCTCCCAGACATCTGTGTACTT-MGB-NFQ
50	TCRBV06-7	730	FAM-TGCTCCCTCTCAGACTCTGTT-MGB-NFQ
50	TCRBV06-8	731	FAM-CCTCCCAGACATCTGTGTACTT-MGB-NFQ
50	TCRBV06-9	732	FAM-TCCCTCCCAGACATCTGTAT-MGB-NFQ
55	TCRBV07-1	733	FAM-AAGTCCAGCGCACACA-MGB-NFQ
55	TCRBV07-2	734	FAM-ATCCAGCGCACACAGCA-MGB-NFQ
55	TCRBV07-3	735	FAM-AAGATCCAGCGCACAGA-MGB-NFQ
55	TCRBV07-4	736	FAM-AAGATCCAGCGCACAGA-MGB-NFQ
55	TCRBV07-5p	737	FAM-ATCCAGCGCACAGAGCAA-MGB-NFQ
60	TCRBV07-6	738	FAM-ATCCAGCGCACAGAGCA-MGB-NFQ
60	TCRBV07-7	739	FAM-ATTCAGCGCACAGAGCA-MGB-NFQ
60	TCRBV07-8	740	FAM-AAGATCCAGCGCACACA-MGB-NFQ
65	TCRBV07-9	741	FAM-ATCCAGCGCACAGAGCA-MGB-NFQ
65	TCRBV08-1p	742	FAM-AACCCTGGAGTCACTAGCA-MGB-NFQ

TABLE 2A-continued

Gene segment	SEQ ID NO:	probe
TCRBV08-2p	743	FAM-AGCCAGACCTATCTGTACCA-MGB-NFQ
TCRBV09	744	FAM-AGCTCTCTGGAGCTGG-MGB-NFQ
TCRBV10-1	745	FAM-CCTCCTCCCAGACATCTGTATA-MGB-NFQ
TCRBV10-2	746	FAM-CGCTCCCAGACATCTGTGTATT-MGB-NFQ
TCRBV10-3	747	FAM-AGCTCCCAGACATCTGTGTACT-MGB-NFQ
TCRBV11-1	748	FAM-AAGATCCAGCCTGCAGAGCTT-MGB-NFQ
TCRBV11-2	749	FAM-ATCCAGCCTGCAGAGCTTGA-MGB-NFQ
TCRBV11-3	750	FAM-AAGATCCAGCCTGCAGAGCTT-MGB-NFQ
TCRBV12-1p	751	FAM-CCAGGGACTTGGGCTATATT-MGB-NFQ
TCRBV12-2p	752	FAM-AAGATCCAGCCTGCAGAGCA-MGB-NFQ
TCRBV12-3	753	FAM-AGGGACTCAGCTGTACTT-MGB-NFQ
TCRBV12-4	754	FAM-AGGGACTCAGCTGTACTT-MGB-NFQ
TCRBV12-5	755	FAM-CCAGGGACTCAGCTGTGTATT-MGB-NFQ
TCRBV13	756	FAM-AACATGAGCTCCTGGAGCT-MGB-NFQ
TCRBV14	757	FAM-TGCAGAACTGGAGGATTCTGGA-MGB-NFQ
TCRBV15	758	FAM-ACGCAGCCATGTACCT-MGB-NFQ
TCRBV16	759	FAM-ATCCAGGCTACGAAGCTTGA-MGB-NFQ
TCRBV17p	760	FAM-AGGGACTCAGCCGTGTATCT-MGB-NFQ
TCRBV18	761	FAM-CGAGGAGATTCCCGCAGCTTATT-MGB-NFQ
TCRBV19	762	FAM-AGAACCCGACAGCTTCT-MGB-NFQ
TCRBV20-1	763	FAM-TCCGAAGACAGCAGCTTCT-MGB-NFQ
TCRBV21-1p	764	FAM-AGATCCAGTCCACGGAGTCA-MGB-NFQ
TCRBV22p	765	FAM-ACACCAGCCAAACAGCTT-MGB-NFQ
TCRBV23-1p	766	FAM-GGCAATCCTGTCCTCAGAA-MGB-NFQ
TCRBV24-1	767	FAM-CCAACCAGACAGCTCTTACT-MGB-NFQ
TCRBV25-1	768	FAM-CCTCACATACTCTCAGTACCT-MGB-NFQ
TCRBV26p	769	FAM-AGCACCAACCAGACATCTGT-MGB-NFQ
TCRBV27-1	770	FAM-CCAACCAGACCTCTGTACTT-MGB-NFQ
TCRBV28	771	FAM-AGCACCAACCAGACATCT-MGB-NFQ
TCRBV29-1	772	FAM-TGAGCAACATGAGCCCTGAA-MGB-NFQ
TCRBV30	773	FAM-TCTTCTCAGTGACTCTGGCTT-MGB-NFQ

In certain embodiments, oligonucleotide probes useful in the methods disclosed herein may be modified, for example, with the ZEN moiety or to contain “locked nucleic acid” (LNA) where the ribose ring is “locked” by a methylene bridge connecting the 2'-O atom and the 4'-C atom (see, Owczarzy et al. 2011 Biochemistry 50(43):9352-67). Both types of oligonucleotides may be obtained from Integrated DNA Technologies, Inc. (IDT, Coralville, Iowa).

To quantitate the amount of specific DNA or RNA in a sample, a standard curve can be generated using standard control DNA (e.g., a plasmid containing the gene(s) of interest, or, as described elsewhere herein, known quantities of purified T cell or B cell DNA). Standard curves are generated using the C_t values determined in the real-time PCR, which are related to the initial template DNA or cDNA concentration used in the assay. Standard dilutions ranging from 10-10⁶ copies of the gene of interest are generally sufficient. In addition, a standard curve is generated for the control sequence. This permits standardization of initial DNA or RNA content of a tissue sample to the amount of control for comparison purposes.

The present methods are highly sensitive and are capable of detecting the presence of 10 or even fewer adaptive immune cells per 10,000 cells in the mixture of cells. In one embodiment, the present methods are capable of detecting the presence of 9, 8, 7, 6, 5, 4, 3, 2, or 1 adaptive immune cell per 10,000 cells in the mixture of cells.

In certain embodiments, the present methods are capable of detecting 10 picograms of adaptive immune cell DNA in a DNA sample extracted from a population of mixed cells. In certain embodiments, the present methods are capable of detecting, 9, 8, 7, 6, or 5 picograms of adaptive immune cell DNA from a source of DNA extracted from a mixed population of cells, such as a tumor sample.

Multiplex Digital PCR

Alternatively, in a related aspect also contemplated herein, digital PCR methods can be used to quantitate the number of target genomes in a sample, without the need for a standard curve. In digital PCR, the PCR reaction for a single sample is performed in a multitude of more than 100 microcells or droplets (also referred to herein as “assay samples”), such that each droplet either amplifies (e.g., generation of an amplification product provides evidence of the presence of at least one template molecule in the microcell or droplet) or fails to amplify (evidence that the template was not present in a given microcell or droplet). Hence, the individual readout signals are qualitative or “digital” in nature. By simply counting the number of positive microcells, it is possible directly to count the number of target genomes that are present in an input sample. Digital PCR methods typically use an endpoint readout, rather than a conventional quantitative PCR signal that is measured after each cycle in the thermal cycling reaction (see, e.g., Vogelstein and Kinzler, 1999 *Proc. Natl. Acad. Sci. USA* 96:9236-41; Pohl and Shih, 2004 *Expert Rev. Mol. Diagn.* 4(1): 41-7, 2004; Pekin et al., 2011 *Lab. Chip* 11(13):2156; Zhong et al., 2011 *Lab. Chip* 11(13):2167; Tewhey et al., 2009 *Nature Biotechnol.* 27:1025; 2010 *Nature Biotechnol.* 28:178). Compared with traditional PCR, dPCR has the following advantages: (1) there is no need to rely on references or standards, (2) desired precision may be achieved by increasing the total number of PCR replicates, (3) it is highly tolerant to inhibitors, (4) it is capable of analyzing complex mixtures, and (5) it provides a linear response to the number of copies present in a sample to allow for small change in the copy number to be detected.

Accordingly, in a related aspect, the present disclosure provides a method for quantifying the relative representation of adaptive immune cells in a test biological sample that comprises a mixture of cells (i.e., both adaptive immune cells and cells that are not adaptive immune cells). The method comprises first distributing test sample template DNA extracted from the test biological sample to form a set of assay samples followed by amplifying the test sample template DNA in the set of assay samples in a multiplex dPCR. The multiplex dPCR comprises (i) a plurality of V-segment oligo-

45

nucleotide primers that are each independently capable of specifically hybridizing to at least one polynucleotide encoding a TCR V-region polypeptide or an Ig V-region polypeptide, wherein each V-segment primer comprises a nucleotide sequence of at least 15 contiguous nucleotides that is complementary to at least one functional TCR or Ig V-encoding gene segment and wherein the plurality of V-segment primers specifically hybridize to substantially all functional TCR or IgV-encoding gene segments that are present in the test sample, and (ii) a plurality of J-segment oligonucleotide primers that are each independently capable of specifically hybridizing to at least one polynucleotide encoding a TCR J-region polypeptide or an Ig J-region polypeptide, wherein each J-segment primer comprises a nucleotide sequence of at least 15 contiguous nucleotides that is complementary to at least one functional TCR or Ig J-encoding gene segment and wherein the plurality of J-segment primers specifically hybridize to substantially all functional TCR or Ig J-encoding gene segments that are present in the test sample. The V-segment and J-segment primers are capable of amplifying in the multiplex dPCR substantially all rearranged TCR or Ig CDR3-encoding regions in the test sample to produce a multiplicity of amplified rearranged DNA molecules from the adaptive immune cells in the test sample. The multiplex dPCR further comprises a set of control primers to produce an internal control gene amplification product, wherein the set of control primers amplifies an internal control gene DNA segment that is not specific to adaptive immune cells. The number of assay samples that detectably contain the amplified rearranged DNA molecules is compared with the number of assay samples that detectably contain the internal control gene amplification product, from which the relative representation of adaptive immune cells in the test biological sample is quantified.

Any of the DNA or RNA extracted from a mixed population of cells from a sample described herein (e.g., samples described in connection with multiplex qPCR), any of the amplified regions described herein (e.g., various CDR3 regions), any of the compositions that comprise multiple of V-segment and J-segment primers provided herein (e.g., those described in connection with multiplex qPCR), any of the methods for detecting amplification products (e.g., using fluorescent probes described in connection with multiplex qPCR), and any of the internal controls common to all of the cells (i.e., in the adaptive immune cells and in the cells that are not adaptive immune cells) in a test biological sample (e.g., the internal controls described in connection with multiplex qPCR) may be used in multiplex dPCR as provided herein.

Unlike qPCR, a known amount of control adaptive immune cell template DNA extracted from a control adaptive immune cell sample is not needed in dPCR. In addition, because dPCR typically uses an endpoint readout, rather than a conventional qPCR signal that is measured after each cycle in the thermal cycling reaction, no standard curve of amplification of adaptive immune cell template DNA is needed. However, in certain embodiments, although not necessary, it is possible that a known amount of control adaptive immune cell template DNA may be amplified separately from template DNA extracted from a test biological sample by qPCR to be used as a positive control for the template DNA extracted from the test biological sample.

As described herein, an internal control gene segment that is not specific to adaptive immune cells may be amplified in a multiplex dPCR. Because the number of copies of the internal control gene segment per cell is known, the number of assay samples that detectably contain the amplification product of

46

the internal control gene segment allows the quantification of the number of the total cells (including adaptive immune cells and those that are not adaptive immune cells) from which test sample template DNA was extracted. If the number of copies of rearranged TCR or Ig CDR3-encoding regions per cell is known (e.g., about 80% of αβ T cells have only one of their two TCRβ alleles rearranged, while the other 20% have both alleles rearranged, with one of the two productive and the other non-productive), comparing the number of assay samples that detectably contain the amplification products of rearranged TCR or Ig CDR3-encoding region with the number of assay samples that detectably contain the amplification product of the internal control gene segment allows quantification of the relative representation of adaptive immune cells (i.e., percentage of the cells in the test biological sample that are adaptive immune cells).

In certain embodiments, a DNA sample (e.g., DNA extracted from a test biological sample described herein) is fractionated by the simple process of dilution so that each fraction contains approximately one copy of DNA template or less. By isolating individual DNA templates, this process effectively enriches DNA molecules that were present at very low levels in the original sample. In certain embodiments, the sample is split into many fractions by dilution so that about 0.1 to about 0.3, about 0.3 to about 0.6, about 0.6 to about 1 copy of DNA per individual reactions.

Any systems known in the art for performing digital PCR methodology may be used in the methods provided herein, for example, the ABI QUANTSTUDIO™12K, Flex System (Life Technologies, Carlsbad, Calif.), the QX100™ DROPLET DIGITAL™ PCR system (BioRad, Hercules, Calif.), the QUANTALIFE™ digital PCR system (BioRad, Hercules, Calif.), or the RAINDANCE™ microdroplet digital PCR system (Raindance Technologies, Lexington, MA).

The present methods using dPCR are highly sensitive and are capable of detecting the presence of 10 or even fewer adaptive immune cells per 10,000 cells in the mixture of cells. In one embodiment, the present methods are capable of detecting the presence of 9, 8, 7, 6, 5, 4, 3, 2, or 1 adaptive immune cell per 10,000 cells in the mixture of cells.

In certain embodiments, the present methods using dPCR are capable of detecting 10 picograms of adaptive immune cell DNA in a DNA sample extracted from a population of mixed cells. In certain embodiments, the present methods are capable of detecting 9, 8, 7, 6, or 5 picograms of adaptive immune cell DNA from a source of DNA extracted from a mixed population of cells, such as a tumor sample.

Methods of Use

The methods described herein may be used to enumerate the relative presence of tumor-infiltrating lymphocytes, or of lymphocytes infiltrating a somatic tissue that is the target of an autoimmune reaction, based on quantification of the relative representation of DNA from such adaptive immune cells in DNA extracted from a biological sample, comprising a mixture of cell types, that has been obtained from such a tumor or tissue. Such methods are useful for determining cancer or autoimmune disease prognosis and diagnosis, for assessing effects of a therapeutic treatment (e.g., assessing drug efficacy and/or dose-response relationships), and for identifying therapeutic courses for cancer treatment, for treatment of autoimmune diseases, or for treatment of transplant rejection, and may find other related uses.

To assess a therapeutic treatment, for example, certain embodiments contemplate a method in which is assessed an effect of the therapeutic treatment on the relative representation of adaptive immune cells in at least one tissue in a subject to whom the treatment has been administered. By way of

illustration and not limitation, according to certain such embodiments a treatment that alters (e.g., increases or decreases in a statistically significant manner) the relative representation of adaptive immune cells in a tissue or tissues may confer certain benefits on the subject. For instance, certain cancer immunotherapies are designed to enhance the number of tumor infiltrating lymphocytes (TIL). It has been shown that the presence of CD3+ TIL in ovarian tumors is strongly correlated with patient outcome (see, e.g., Hwang et al., 2011 *Gynecol. Oncol.*, 124(2):192). Further data clarified that in addition to TIL presence, the characteristics of the TIL populations were also significant: CD8+ TILs and clonal TILs were associated with longer Disease Free Survival (DFS), and infiltrating regulatory T cells were associated with shorter DFS (see, Stumpf et al., 2009 *Br. J. Cancer* 101:1513-21). These studies indicated that TIL may be an independent prognostic factor (see, Clarke et al., 2009 *Mod. Pathol.* 22:393-402). Thus, quantification of the relative representation of adaptive immune cell DNA as described herein, for purposes of detecting possible increases in TIL in tumor tissue samples obtained at one or a plurality of time points before treatment, during the course of treatment and/or following treatment may provide highly useful information with respect to determining efficacy of the treatment, and therefrom developing a prognosis for the subject.

As another example, certain autoimmune disease-directed immunotherapies are designed to reduce the number of tissue infiltrating lymphocytes in one or more afflicted tissues such as tissues or organs that may be targets of clinically inappropriate autoimmune attack, such that quantification of the relative representation of adaptive immune cell DNA as described herein, for purposes of detecting possible decreases in adaptive immune cells in tissue samples obtained at one or a plurality of time points before treatment, during the course of treatment and/or following treatment may provide highly useful information with respect to determining efficacy of the treatment, and therefrom developing a prognosis for the subject.

As a further example, certain transplant rejection-directed immunotherapies are designed to reduce the number of tissue infiltrating lymphocytes in transplanted organs, such that quantification of the relative representation of adaptive immune cell DNA as described herein, for purposes of detecting possible decreases in adaptive immune cells in tissue samples from transplanted organs obtained at one or a plurality of time points before treatment, during the course of treatment and/or following treatment may provide highly useful information with respect to determining efficacy of the treatment, and therefrom developing a prognosis for the subject.

In these and related embodiments, the herein described methods for quantifying the relative representation of adaptive immune cell DNA may be practiced using test biological samples obtained from a subject at one or a plurality of time points prior to administering the therapeutic treatment to the subject, and at one or a plurality of time points after administering the therapeutic treatment to the subject. The samples may be obtained from the same or from different tissues, which may vary as a function of the particular condition of the subject. For example, by way of illustration and not limitation, in the case of an inoperable tumor the test biological samples that are obtained from the subject before and after treatment may be from the same tissue, whereas in the case of a tumor that is partially removed surgically, or that occurs at multiple sites in the subject, the test biological samples may

be obtained from different tissues or from different tissue sites before and after the therapeutic treatment is administered.

Also contemplated herein are embodiments in which any of the herein described methods may further comprise determination of the relative structural diversity of adaptive immune receptors (e.g., the sequence diversity among products of productively rearranged TCR and/or immunoglobulin genes) in the adaptive immune cell component of the mixture of cells that is present in the test biological sample. In certain such embodiments, the present qPCR methodologies using the herein described rearranged adaptive immune receptor encoding specific oligonucleotide primer sets permit ready identification of the particular primer combinations that generate the production of amplified rearranged DNA molecules. Accordingly, for example, these embodiments permit determination of the relative degree of clonality of an adaptive immune cell population that is present as part of a mixed cell population in a test biological sample, which may have prognostic value.

For instance, in a solid tumor sample in which TILs are detected by quantifying the relative representation of adaptive immune cell DNA in DNA extracted from the sample as described herein, the present methods contemplate determination of whether only one or a few (e.g., no more than 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10) combinations of a particular V-segment oligonucleotide primer and a particular J-segment oligonucleotide primer are predominantly (e.g., generating at least 80, 85, 90, 95, 97 or 99 percent of amplification products) responsible for the PCR production of amplified rearranged adaptive immune cell DNA molecules. Such an observation of one or a few predominant adaptive immune receptor gene-encoding amplification product would, according to non-limiting theory, indicate a low degree of TIL heterogeneity. Conversely, determination of a high degree of heterogeneity in adaptive immune receptor structural diversity by characterization of TIL DNA would indicate that a predominant TIL clone is not present.

40 Sequencing

It is thus further contemplated for these and related embodiments of any of the herein described methods that such a method may, optionally, further comprise sequencing the amplified adaptive immune receptor encoding DNA molecules that are produced. In certain embodiments, at least 30, 40, 50, 60, 70, 80, 90, 100, 101-150, 151-200, 201-300, 301-500, and not more than 1000 contiguous nucleotides of the amplified adaptive immune receptor encoding DNA molecules are sequenced. Compositions and methods for the sequencing of rearranged adaptive immune receptor gene sequences and for adaptive immune receptor clonotype determination are described in Robins et al., 2009 *Blood* 114, 4099; Robins et al., 2010 *Sci. Translat. Med.* 2:47ra64; Robins et al., 2011 *J. Immunol. Meth.* doi:10.1016/j.jim.2011.09.001; Sherwood et al. 2011 *Sci. Translat. Med.* 3:90ra61; U.S. application Ser. No. 13/217,126 (US Pub. No. 2012/0058902), U.S. application Ser. No. 12/794,507 (US Pub. No. 2010/0330571), WO/2010/151416, WO/2011/106738 (PCT/US2011/026373), WO2012/027503 (PCT/US2011/049012), U.S. application Ser. No. 61/550,311, and U.S. application Ser. No. 61/569,118, herein incorporated by reference.

Another embodiment is the method further comprising a step of sequencing the amplified DNA molecules. Another embodiment is wherein the sequencing step utilizes a set of sequencing oligonucleotides that hybridize to regions within the amplified DNA molecules.

Sequencing may be performed using any of a variety of available high through-put single molecule sequencing machines and systems. Illustrative sequence systems include sequence-by-synthesis systems such as the Illumina Genome Analyzer and associated instruments (Illumina, Inc., San Diego, Calif.), Helicos Genetic Analysis System (Helicos BioSciences Corp., Cambridge, Mass.), Pacific Biosciences PacBio RS (Pacific Biosciences, Menlo Park, Calif.), or other systems having similar capabilities. Sequencing is achieved using a set of sequencing oligonucleotides that hybridize to a defined region within the amplified DNA molecules. The sequencing oligonucleotides are designed such that the V- and J-encoding gene segments can be uniquely identified by the sequences that are generated, based on the present disclosure and in view of known adaptive immune receptor gene sequences that appear in publicly available databases.

The term "gene" means the segment of DNA involved in producing a polypeptide chain such as all or a portion of a TCR or Ig polypeptide (e.g., a CDR3-containing polypeptide); it includes regions preceding and following the coding region "leader and trailer" as well as intervening sequences (introns) between individual coding segments (exons), and may also include regulatory elements (e.g., promoters, enhancers, repressor binding sites and the like), and may also include recombination signal sequences (RSSs) as described herein.

The nucleic acids of the present embodiments, also referred to herein as polynucleotides, may be in the form of RNA or in the form of DNA, which DNA includes cDNA, genomic DNA, and synthetic DNA. The DNA may be double-stranded or single-stranded, and if single stranded may be the coding strand or non-coding (anti-sense) strand. A coding sequence which encodes a TCR or an immunoglobulin or a region thereof (e.g., a V region, a D segment, a J region, a C region, etc.) for use according to the present embodiments may be identical to the coding sequence known in the art for any given TCR or immunoglobulin gene regions or polypeptide domains (e.g., V-region domains, CDR3 domains, etc.), or may be a different coding sequence, which, as a result of the redundancy or degeneracy of the genetic code, encodes the same TCR or immunoglobulin region or polypeptide.

In certain embodiments, the amplified J-region encoding gene segments may each have a unique sequence-defined identifier tag of 2, 3, 4, 5, 6, 7, 8, 9, 10 or about 15, 20 or more nucleotides, situated at a defined position relative to a RSS site. For example, a four-base tag may be used, in the J β -region encoding segment of amplified TCR β CDR3-encoding regions, at positions +11 through +14 downstream from the RSS site. However, these and related embodiments need not be so limited and also contemplate other relatively short nucleotide sequence-defined identifier tags that may be detected in J-region encoding gene segments and defined based on their positions relative to an RSS site. These may vary between different adaptive immune receptor encoding loci.

The recombination signal sequence (RSS) consists of two conserved sequences (heptamer, 5'-CACAGTG-3', and nonamer, 5'-ACAAAAAACC-3'), separated by a spacer of either 12+/-1 bp ("12-signal") or 23+/-1 bp ("23-signal"). A number of nucleotide positions have been identified as important for recombination including the CA dinucleotide at position one and two of the heptamer, and a C at heptamer position three has also been shown to be strongly preferred as well as an A nucleotide at positions 5, 6, 7 of the nonamer. (Ramsden et. al 1994; Akamatsu et. al 1994; Hesse et. al. 1989). Mutations of other nucleotides have minimal or inconsistent effects. The spacer, although more variable, also has an

impact on recombination, and single-nucleotide replacements have been shown to significantly impact recombination efficiency (Fanning et. al. 1996; Larijani et. al 1999; Nadel et. al. 1998). Criteria have been described for identifying RSS 5 polynucleotide sequences having significantly different recombination efficiencies (Ramsden et. al 1994; Akamatsu et. al. 1994; Hesse et. al. 1989 and Cowell et. al. 1994). Accordingly, the sequencing oligonucleotides may hybridize adjacent to a four base tag within the amplified J-encoding 10 gene segments at positions +11 through +14 downstream of the RSS site. For example, sequencing oligonucleotides for TCRB may be designed to anneal to a consensus nucleotide motif observed just downstream of this "tag", so that the first four bases of a sequence read will uniquely identify the J-encoding gene segment (Table 2B).

TABLE 2B

Sequencing oligonucleotides			
	SEQ	ID	NO: Oligonucleotide sequence
20	Jseq 1-1	884	ACAACTGTGAGTCTGGTGCCTTGTC CAAAGAAA
25	Jseq 1-2	885	ACAAACGGTTAACCTGGTCCCCGAACCGAAGGTG
	Jseq 1-3	886	ACAAACAGTGAGGCCACTTCCCCTCTCC AAAAATAT
	Jseq 1-4	887	AAGACAGAGAGCTGGGTTCCACTGCC AAAAAAC
30	Jseq 1-5	888	AGGATGGAGAGTCGAGTCCCCTCACCA AAATGC
	Jseq 1-6	889	GTCACAGTGAGCCTGGTCCCCTCC AAAGTGG
	Jseq 2-1	890	AGCACCGTGAGCCGTGTCCTGGCC GAAGAAC
35	Jseq 2-2	891	AGTACCGGTAGCCCTAGAGCCTTCTCC AAAAAAC
	Jseq 2-3	892	AGCACTGTAGCCGGGTGCCTGGGCC AAAAATAC
	Jseq 2-4	893	AGCACTGAGAGCCGGTCCGGCGCC GAAGTAC
40	Jseq 2-5	894	AGCACCCAGGAGCCCGTGCCTGGCC GAAGTAC
	Jseq 2-6	895	AGCACCGGTAGCCCTGGTGC CCGGCCCGAAGTAC
	Jseq 2-7	896	GTGACCGTGAGCCCTGGTGC CCGGCCCGAAGTAC

45 The information used to assign identities to the J- and V-encoding segments of a sequence read is entirely contained within the amplified sequence, and does not rely upon the identity of the PCR primers. In particular, the methods described herein allow for the amplification of all possible V-J 50 combinations at a TCR or Ig locus and sequencing of the individual amplified molecules allows for the identification and quantitation of the uniquely rearranged DNA encoding the CDR3 regions. The diversity of the adaptive immune cells of a given sample can be inferred from the sequences generated 55 using the methods and algorithms described herein. One surprising advantage provided in certain preferred embodiments by the compositions and methods of the present disclosure was the ability to amplify successfully all possible V-J combinations of an adaptive immune cell receptor locus in a single multiplex PCR reaction.

In certain embodiments, the sequencing oligonucleotides described herein may be selected such that promiscuous priming of a sequencing reaction for one J-encoding gene segment by an oligonucleotide specific to another distinct 60 J-encoding gene segment generates sequence data starting at exactly the same nucleotide as sequence data from the correct sequencing oligonucleotide. In this way, promiscuous

annealing of the sequencing oligonucleotides does not impact the quality of the sequence data generated.

The average length of the CDR3-encoding region, for the TCR, defined as the nucleotides encoding the TCR polypeptide between the second conserved cysteine of the V segment and the conserved phenylalanine of the J segment, is 35 \pm 3 nucleotides. Accordingly and in certain embodiments, PCR amplification using V-segment oligonucleotide primers with J-segment oligonucleotide primers that start from the J segment tag of a particular TCR or IgH J region (e.g., TCR J β , TCR J γ or IgH JH as described herein) will nearly always capture the complete V-D-J junction in a 50 base pair read. The average length of the IgH CDR3 region, defined as the nucleotides between the conserved cysteine in the V segment and the conserved phenylalanine in the J segment, is less constrained than at the TCR β locus, but will typically be between about 10 and about 70 nucleotides. Accordingly and in certain embodiments, PCR amplification using V-segment oligonucleotide primers with J-segment oligonucleotide primers that start from the IgH J segment tag will capture the complete V-D-J junction in a 100 base pair read.

PCR primers that anneal to and support polynucleotide extension on mismatched template sequences are referred to as promiscuous primers. In certain embodiments, the TCR and Ig J-segment reverse PCR primers may be designed to minimize overlap with the sequencing oligonucleotides, in order to minimize promiscuous priming in the context of multiplex PCR. In one embodiment, the TCR and Ig J-segment reverse primers may be anchored at the 3' end by annealing to the consensus splice site motif, with minimal overlap of the sequencing primers. Generally, the TCR and Ig V and J-segment primers may be selected to operate in PCR at consistent annealing temperatures using known sequence/primer design and analysis programs under default parameters.

For the sequencing reaction, the exemplary IGHJ sequencing primers extend three nucleotides across the conserved CAG sequences as shown in Table 2C.

TABLE 2C

IgH J segment	SEQ ID NO : Sequence
>IGHJSEQ4_1	897 TGAGGGAGACGGTGACCAGGGTCCCTGGCCCCAG
>IGHJSEQ4_3	898 TGAGGGAGACGGTGACCAGGGTCCCTGGCCCCAG
>IGHJSEQ4_2	899 TGAGGGAGACGGTGACCAGGGTCCCTGGCCCCAG
>IGHJSEQ3_1	900 CTGAAGAGAGACGGTGACCATTGTCCTGGCCCCCA
2	G
>IGHJSEQ6_1	901 CTGAGGGAGACGGTGACCCTGGCCCCCA
	G
>IGHJSEQ6_2	902 TGAGGGAGACGGTGACCCTGGCCCCCA
>IGHJSEQ6_3	903 CTGAGGGAGACGGTGACCCTGGCCCCCA
4	G
>IGHJSEQ2_1	904 CTGAGGGAGACGGTGACCAGGGTCCCTGGCCCCCA
	G
>IGHJSEQ5_1	905 CTGAGGGAGACGGTGACCAGGGTCCCTGGCCCCCA
	G
>IGHJSEQ5_2	906 CTGAGGGAGACGGTGACCAGGGTCCCTGGCCCCCA
	G

TABLE 2C-continued

IgH J segment	SEQ ID NO : Sequence
5	>IGHJSEQ1_1 907 CTGAGGGAGACGGTGACCAGGGTCCCTGGCCCCAG

10 As presently disclosed there are also provided methods for analyzing the sequences of the diverse pool of uniquely rearranged CDR3-encoding regions that are generated using the compositions and methods that are described herein. In particular, an algorithm is provided to correct for PCR bias, 15 sequencing and PCR errors and for estimating true distribution of specific clonotypes (e.g., a TCR or Ig having a uniquely rearranged CDR3 sequence) in blood or in a sample derived from other peripheral tissue or bodily fluid. A preferred algorithm is described in further detail herein. As 20 would be recognized by the skilled person, the algorithms provided herein may be modified appropriately to accommodate particular experimental or clinical situations.

The use of a PCR step to amplify the TCR or Ig CDR3 regions prior to sequencing could potentially introduce a 25 systematic bias in the inferred relative abundance of the sequences, due to differences in the efficiency of PCR amplification of CDR3 regions utilizing different V and J gene segments. As discussed in more detail in the Examples, each cycle of PCR amplification potentially introduces a bias of 30 average magnitude $1.5^{1/15}=1.027$. Thus, the 25 cycles of PCR introduces a total bias of average magnitude $1.027^{25}=1.95$ in the inferred relative abundance of distinct CDR3 region sequences.

Sequenced reads are filtered for those including CDR3 35 sequences. Sequencer data processing involves a series of steps to remove errors in the primary sequence of each read, and to compress the data. A complexity filter removes approximately 20% of the sequences that are misreads from the sequencer. Then, sequences were required to have a minimum of a six base match to both one of the TCR or Ig J-regions and one of V-regions. Applying the filter to the control lane containing phage sequence, on average only one sequence in 7-8 million passed these steps. Finally, a nearest neighbor algorithm is used to collapse the data into unique 45 sequences by merging closely related sequences, in order to remove both PCR error and sequencing error.

Analyzing the data, the ratio of sequences in the PCR product are derived working backward from the sequence data before estimating the true distribution of clonotypes 50 (e.g., unique clonal sequences) in the blood. For each sequence observed a given number of times in the data herein, the probability that that sequence was sampled from a particular size PCR pool is estimated. Because the CDR3 regions sequenced are sampled randomly from a massive pool of PCR 55 products, the number of observations for each sequence are drawn from Poisson distributions. The Poisson parameters are quantized according to the number of T cell genomes that provided the template for PCR. A simple Poisson mixture model both estimates these parameters and places a pairwise 60 probability for each sequence being drawn from each distribution. This is an expectation maximization method which reconstructs the abundances of each sequence that was drawn from the blood.

To estimate the total number of unique adaptive immune 65 receptor CDR3 sequences that are present in a sample, a computational approach employing the “unseen species” formula may be employed (Efron and Thisted, 1976 *Biometrika*

63, 435-447). This approach estimates the number of unique species (e.g., unique adaptive immune receptor sequences) in a large, complex population (e.g., a population of adaptive immune cells such as T cells or B cells), based on the number of unique species observed in a random, finite sample from a population (Fisher et al., 1943 *J. Anim. Ecol.* 12:42-58; Ionita-Laza et al., 2009 *Proc. Nat. Acad. Sci. USA* 106:5008). The method employs an expression that predicts the number of “new” species that would be observed if a second random, finite and identically sized sample from the same population were to be analyzed. “Unseen” species refers to the number of new adaptive immune receptor sequences that would be detected if the steps of amplifying adaptive immune receptor-encoding sequences in a sample and determining the frequency of occurrence of each unique sequence in the sample were repeated an infinite number of times. By way of non-limiting theory, it is operationally assumed for purposes of these estimates that adaptive immune cells (e.g., T cells, B cells) circulate freely in the anatomical compartment of the subject that is the source of the sample from which diversity is being estimated (e.g., blood, lymph, etc.).

To apply this formula, unique adaptive immune receptors (e.g., TCR β , TCR α , TCR γ , TCR δ , IgH) clonotypes takes the place of species. The mathematical solution provides that for S, the total number of adaptive immune receptors having unique sequences (e.g., TCR β , TCR γ , IgH “species” or clonotypes, which may in certain embodiments be unique CDR3 sequences), a sequencing experiment observes x_s copies of sequence s. For all of the unobserved clonotypes, x_s equals 0, and each TCR or Ig clonotype is “captured” in the course of obtaining a random sample (e.g., a blood draw) according to a Poisson process with parameter λ_s . The number of T or B cell genomes sequenced in the first measurement is defined as 1, and the number of T or B cell genomes sequenced in the second measurement is defined as t.

Because there are a large number of unique sequences, an integral is used instead of a sum. If $G(\lambda)$ is the empirical distribution function of the parameters $\lambda_1, \dots, \lambda_S$, and n_x is the number of clonotypes (e.g., unique TCR or Ig sequences, or unique CDR3 sequences) observed exactly x times, then the total number of clonotypes, i.e., the measurement of diversity E, is given by the following formula (I):

$$E(n_x) = S \int_0^{\infty} \left(\frac{e^{-\lambda} \lambda^x}{x!} \right) dG(\lambda). \quad (\text{I})$$

Accordingly, formula (I) may be used to estimate the total diversity of species in the entire source from which the identically sized samples are taken. Without wishing to be bound by theory, the principle is that the sampled number of clonotypes in a sample of any given size contains sufficient information to estimate the underlying distribution of clonotypes in the whole source. The value for $\Delta(t)$, the number of new clonotypes observed in a second measurement, may be determined, preferably using the following equation (II):

$$\begin{aligned} \Delta(t) &= \sum_x E(n_x)_{msmt1+msmt2} - \sum_x E(n_x)_{msmt1} \\ &= S \int_0^{\infty} e^{-\lambda} (1 - e^{-\lambda t}) dG(\lambda) \end{aligned} \quad (\text{II})$$

in which msmt1 and msmt2 are the number of clonotypes from measurements 1 and 2, respectively. Taylor expansion of $1 - e^{-\lambda t}$ and substitution into the expression for $\Delta(t)$ yields:

$$\Delta(t) = E(x_1)t - E(x_2)t^2 + E(x_3)t^3 - \dots, \quad (\text{iii})$$

which can be approximated by replacing the expectations ($E(n_x)$) with the actual numbers sequences observed exactly x times in the first sample measurement. The expression for $\Delta(t)$ oscillates widely as t goes to infinity, so $\Delta(t)$ is regularized to produce a lower bound for $\Delta(\infty)$, for example, using the Euler transformation (Efron et al., 1976 *Biometrika* 63:435).

In certain embodiments, there is provided a method for quantifying the relative representation of adaptive immune cells in a mixture of cells in a biological sample, comprising: (a) amplifying DNA extracted from the mixture of cells with a plurality of V segment primers and a plurality of J segment primers in a quantitative polymerase chain reaction (qPCR), wherein the plurality of V segment primers and the plurality of J segment primers permit amplification of substantially all combinations of the V and J segments of a rearranged immune receptor locus; (b) measuring in real time an amount of DNA amplified in (a) by the plurality of V segment primers and the plurality of J segment primers; (c) comparing the amount of amplified DNA measured in (b) to a known amount of adaptive immune cell DNA that has been amplified by the plurality of V segment primers and the plurality of J segment primers, and therefrom determining an amount of adaptive immune cell DNA extracted from the mixture of cells; and (d) quantifying, from the amount of adaptive immune cell DNA of (c), the relative number of adaptive immune cells in the mixture of cells.

In certain other embodiments, there is provided a method for quantifying the relative representation of adaptive immune cells in a mixture of cells in a biological sample, comprising: (a) amplifying DNA extracted from the mixture of cells with a plurality of V segment primers and a plurality of J segment primers in a dPCR, wherein the plurality of V segment primers and the plurality of J segment primers permit amplification of substantially all combinations of the V and J segments of a rearranged immune receptor locus; and (b) comparing the number of assay samples that detectably contain amplified DNA of (a) to the number of assay samples that detectably contain an amplification product of an internal control gene segment, and therefrom determining the relative representation of adaptive immune cells in the mixture of cells.

According to certain herein expressly disclosed embodiments, there are also presently provided methods in which the degree of clonality of adaptive immune cells that are present in a sample, such as a sample that comprises a mixture of cells only some of which are adaptive immune cells, can be determined advantageously without the need for cell sorting or for DNA sequencing. These and related embodiments overcome the challenges of efficiency, time and cost that, prior to the present disclosure, have hindered the ability to determine whether adaptive immune cell presence in a sample (e.g., TIL) is monoclonal or oligoclonal (e.g., whether all TILs are the progeny of one or a relatively limited number of adaptive immune cells), or whether instead adaptive immune cell presence in the sample is polyclonal (e.g., TILs are the progeny of a relatively large number of adaptive immune cells).

According to non-limiting theory, these embodiments exploit current understanding in the art (also described above) that once an adaptive immune cell (e.g., a T or B lymphocyte) has rearranged its adaptive immune receptor-encoding (e.g., TCR or Ig) genes, its progeny cells possess the same adaptive

immune receptor-encoding gene rearrangement, thus giving rise to a clonal population that can be uniquely identified by the presence therein of rearranged CDR3-encoding V- and J-gene segments that may be amplified by a specific pairwise combination of V- and J-specific oligonucleotide primers as herein disclosed.

In such presently disclosed embodiments, qPCR or dPCR may be practiced using specifically selected subsets of the adaptive immune receptor-encoding gene V- and J-segment specific oligonucleotide primers as described herein, to determine a degree of adaptive immune cell clonality in a biological sample. For example, in certain embodiments, separate amplification reactions are set up for a plurality of replicate samples of template DNA that has been extracted from a complex biological sample comprising a heterogeneous mixture of cells (e.g., a solid tumor sample containing tumor cells, mesenchymal cells and TILs). A complete set of TCR J region specific primers is added to every replicate sample, but each replicate sample receives only one TCR V region specific primer. Quantitative PCR amplification is then permitted to proceed, and each replicate sample is quantitatively assessed for the presence or absence of amplification products. The relative representation of amplification products that is generated in each separate reaction, using each particular primer combination, indicates the relative abundance in the sample template DNA of TCR-encoding DNA containing the V-J rearrangement that is capable of being amplified by a specific V-J primer pair that is present in the reaction. The relative abundance of each amplification product reflects the relative representation of T cells of distinct clonal origin in the biological sample.

In certain other embodiments, separate amplification reactions (e.g., qPCR or dPCR) are set up for multiple replicate samples of template DNA extracted from a test biological sample. A complete set of TCR J region specific primers is added to every replicate sample, but each replicate sample receives a subgroup of TCR V region specific primers. Exemplary subgroups of TCR V region specific primers include those provided in Example 5. The relative representation of amplification products generated in each separate reaction, using each particular primer combination, indicates the relative abundance in the sample template DNA of TCR-encoding DNA containing the V-J rearrangements capable of being amplified by specific V-J primer pairs present in the reaction.

In certain embodiments, the methods for quantifying the relative representation of adaptive immune cells in a test biological sample further comprise quantifying the relative representation of CD4+ adaptive immune cells and/or CD8+ adaptive immune cells. Similarly, in certain embodiments, the methods for assessing an effect of a therapeutic treatment on relative representation of adaptive immune cells disclosed herein further comprise assessing an effect of a therapeutic treatment on relative representation of CD4+ adaptive immune cells and/or on relative representation of CD8+ adaptive immune cells.

The human cellular adaptive immune system is mediated by two primary types of T cells, killer T cells and helper T cells. Killer T cells, marked by the surface expression of CD8, recognize short peptides (about 8-10 amino acids) presented on the surface of cells by human leukocyte antigen (HLA Class I molecules). Helper T cells, marked by the surface expression of CD4, recognize longer peptides (about 12-16 amino acids) presented on the surface of cells by HLA Class II molecules. Both of these T cell types derive from a common progenitor cell type.

During the development of T cells in the thymus, the DNA coding for the alpha and beta chains of the Y-like T cell

receptors (TCR) rearrange in a pseudo-random process to form an enormous variety of TCRs. TCR sequence diversity is primarily contained in the complementarity determining region 3 (CDR3) loops of the α and β chains, which bind to the peptide antigen, conveying specificity. The nucleotide sequences that encode the CDR3 loops are generated by V(D)J recombination: variable (V_β), diversity (D_β) and joining (J_β) genes in the genome are rearranged to form a β chain, while V_α and J_α genes rearrange to form an α chain.

After the alpha and beta chains rearrange, while still in the thymus, T cells are both positively and negatively selected against self peptides displayed by Class I and Class II HLA molecules. If a TCR binds strongly to a self peptide:HLA complex, the T cell usually dies. Additionally, a T cell is positively selected, requiring some minimal threshold of binding to either a Class I or Class II presented peptide. Prior to selection, T cells express both CD4 and CD8 on their surface, and are referred to as double positive T cells. Upon positive selection the T cell halts expression of one of these two surface proteins, leaving a single positive T cell committed as either a helper or killer T cell. These two T cell types serve very different functional roles.

The present inventors have discovered that the TCR sequences from, respectively, helper and killer T cells, preferentially utilize different V_β gene segments (see, Example 6). For example, 21 of 48 V_β segments measured have differential usage between CD4+ and CD8+ samples. Exemplary V_β segments preferentially used by CD4+ cells and exemplary V_β segments preferentially used by CD8+ cells include the following:

V β segments more frequent in:	
CD4+ T cells	CD8+ T cells
TRBV11-1***	TRBV10-2*
TRBV18***	TRBV13***
TRBV30*	TRBV16*
TRBV5-1***	TRBV19**
TRBV5-4***	TRBV4-1**
TRBV5-7***	TRBV4-2*
TRBV7-2***	TRBV4-3**
TRBV7-3*	TRBV6-1***
TRBV7-7*	TRBV6-4***
	TRBV7-6***
	TRBV7-8**
	TRBV7-9***

*p < 0.05

**p < 0.01

***p < 0.001

Based on knowledge about such preferential use of different V_β gene segments in a subject, the relative representation in a sample of CD4+ adaptive immune cells and/or CD8+ adaptive immune cells may be quantified. For example, the frequency with which productively rearranged TCR sequences use each V_β segment may be calculated in one or more CD4+ samples isolated from a subject (e.g., a sorted peripheral blood cell population containing predominantly CD4+ T cells, as may be obtained by fluorescence activated cell sorting (FACS) or with anti-CD4 antibody-coated immunomagnetic beads or by other techniques). Similarly, the frequency with which productively rearranged TCR sequences use each V_β segment may be calculated in one or more CD8+ samples from the subject. Such frequencies may be used to train a likelihood model (e.g., a computer program), which may in turn be used to estimate the proportion of CD4+ cells in a sample from the subject having an unknown proportion of CD4+ cells (e.g., a sample of mixed cell types that is obtained

from a solid tumor or from a solid tissue organ) based on the information (e.g., partial or complete sequences) used to train the model with respect to utilization of particular rearranged DNA molecules in the CD4+ and CD8+ compartments, which information is obtained by amplification according to the methods described herein using qPCR or dPCR.

For example, rearranged TCR V β segments amplified by qPCR or dPCR as described herein may be sequenced, and the resulting sequences may be used to estimate the proportion of CD4+ cells or CD8+ cells using a likelihood model developed as described herein. Alternatively, primers specific for TCR V β gene segments that are preferentially used in CD4+ adaptive immune cells may be grouped together to form one or more subgroups of primers ("first subgroups"), while primers specific for V β gene segments preferentially used in CD8+ adaptive immune cells may form one or more other subgroups ("second subgroups"). Multiple qPCR or dPCR reactions are performed individually, each using primers of only one of the first subgroups or one of the second subgroups. For qPCR, the amounts of amplification products using primers from the first subgroups of primers and from the second subgroups are separately measured. Similarly, for dPCR, the numbers of assay samples that detectably contain amplified rearranged DNA molecules using primers from the first subgroups of primers and from the second subgroups are separately measured. The amounts of amplification products from qPCR reactions and the numbers of assay samples from dPCR reactions may then be used to estimate the proportion of CD4+ cells or CD8+ cells using the likelihood model.

In certain embodiments, the preferential usage of different V β gene segments in a subject (e.g., a patient) may be determined by sorting cells from the subject (e.g., blood cells) into CD4+ cells and CD8+ cells followed by measuring the frequency of each rearranged TCR sequence in the CD4+ cells and CD8+ cells. The frequencies of rearranged TCR sequences in the CD4+ cells and CD8+ cells may be used to develop a possibility or probability model. A test biological sample from the same subject may then be used to isolate genomic DNA and is used as a template in amplifying rearranged TCR loci by qPCR or dPCR according to the methods described herein. The information about the amplified rearranged adaptive TCR loci (e.g., their sequences or their types based on specific primers or specific groups of primers used in amplification reactions) may then be used to estimate the proportion of CD4+ cells or CD8+ cells in the test biological sample. Using the frequencies of particular rearranged TCR sequences in known CD4+ cells and CD8+ cells (e.g., FACS-sorted peripheral blood cells) of the same subject from which the test biological sample is also obtained may avoid or reduce the observed variability in CD4+-specific or CD8+-specific preferential use of different V β gene segments among different subjects.

It will be appreciated by the skilled person based on the present disclosure that variations and permutations of the assay design may be practiced, such as setting up parallel reactions in which every reaction contains template DNA from the mixed cell-type sample and a complete complement of V region primers but only one J region primer, or reactions that contain different known subsets of V and/or J region primers. As another example, replicate qPCR or dPCR amplification reactions may be set up that each contain template DNA from the mixed cell-type sample and a full complement of V and J region oligonucleotide primers such as those disclosed herein, and each individual reaction also contains a single, different detectably labeled V region probe such as one of the labeled probes presented in Table 2A, or a different subset of the labeled probes presented in Table 2A (e.g., 1, 2,

3, 4, 5, 6, 7, 8, 9 or 10 different detectably labeled V region probes from Table 2A). Detection of the presence of amplification products in one or more particular reactions permits determination of the degree of adaptive immune cell clonality in the sample from which template DNA was obtained.

The degree of adaptive immune cell clonality in a sample may in this manner be readily determined, without requiring isolation and sorting of adaptive immune cells, and without requiring (although not precluding, as provided by certain 10 herein disclosed embodiments) DNA sequencing. In a solid tissue tumor sample containing TILs, for example, these and related embodiments permit determination of whether the TIL population is predominantly monoclonal or oligoclonal and thus represents a relatively small number of clones that 15 have undergone extensive expansion via cellular (clonal) proliferation, or whether instead the TIL population is clonally diverse and thus heterogeneous with respect to adaptive immune receptor utilization. Information from such analyses will usefully provide information concerning the physiological 20 and pathological status of the tissue (and hence of the source subject), and will be particularly useful in situations where samples obtained before, during and/or after therapy are assayed, according to certain embodiments described elsewhere herein. For instance, the degree of TIL clonality in 25 a tumor tissue may provide diagnostic and/or prognostic information, including information regarding the potential efficacy of a therapeutic regimen or regarding the optimal dosing regimen. Similarly, the degree of TIL clonality in a tissue that is a target of autoimmune attack may usefully 30 permit identification and refinement of clinical approaches to autoimmune disease.

Also provided herein according to certain embodiments is a method for determining a course of treatment for a patient in need thereof, comprising quantifying the relative representation 35 of tumor-infiltrating lymphocytes or lymphocytes infiltrating a somatic tissue that is the target of an autoimmune reaction, using the methods described herein. In this regard, the patient in need thereof may be a cancer patient or a patient having an autoimmune disease. In certain embodiments, a 40 patient may have a cancer including, but not limited to, colorectal, hepatocellular, gallbladder, pancreatic, esophageal, lung, breast, prostate, skin (e.g., melanoma), head and neck, renal cell carcinoma, ovarian, endometrial, cervical, bladder and urothelial cancer. In certain other embodiments, a patient 45 may have an organ transplant, such as a liver transplant, a lung transplant, a kidney transplant, a heart transplant, a spleen transplant, a pancreas transplant, a skin transplant/graft, an intestine transplant, and a thymus transplant.

Autoimmune diseases include, but are not limited to, 50 arthritis (including rheumatoid arthritis, reactive arthritis), systemic lupus erythematosus (SLE), psoriasis, inflammatory bowel disease (IBD) (including ulcerative colitis and Crohn's disease), encephalomyelitis, uveitis, myasthenia gravis, multiple sclerosis, insulin dependent diabetes, Addison's disease, celiac disease, chronic fatigue syndrome, 55 autoimmune hepatitis, autoimmune alopecia, ankylosing spondylitis, fibromyalgia, pemphigus vulgaris, Sjogren's syndrome, Kawasaki's Disease, hyperthyroidism/Graves disease, hypothyroidism/Hashimoto's disease, endometriosis, scleroderma, pernicious anemia, Goodpasture syndrome, 60 Guillain-Barré syndrome, Wegener's disease, glomerulonephritis, aplastic anemia (including multiply transfused aplastic anemia patients), paroxysmal nocturnal hemoglobinuria, idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, Evan's syndrome, Factor VIII inhibitor 65 syndrome, systemic vasculitis, dermatomyositis, polymyositis and rheumatic fever, autoimmune lymphoproliferative

syndrome (ALPS), autoimmune bullous pemphigoid, Parkinson's disease, sarcoidosis, vitiligo, primary biliary cirrhosis, and autoimmune myocarditis.

The practice of certain embodiments of the present invention will employ, unless indicated specifically to the contrary, conventional methods in microbiology, molecular biology, biochemistry, molecular genetics, cell biology, virology and immunology techniques that are within the skill of the art, and reference to several of which is made below for the purpose of illustration. Such techniques are explained fully in the literature. See, e.g., Sambrook, et al., *Molecular Cloning: A Laboratory Manual* (3rd Edition, 2001); Sambrook, et al., *Molecular Cloning: A Laboratory Manual* (2nd Edition, 1989); Maniatis et al., *Molecular Cloning: A Laboratory Manual* (1982); Ausubel et al., *Current Protocols in Molecular Biology* (John Wiley and Sons, updated July 2008); *Short Protocols in Molecular Biology: A Compendium of Methods from Current Protocols in Molecular Biology*, Greene Pub. Associates and Wiley-Interscience; Glover, *DNA Cloning: A Practical Approach*, vol. I & II (IRL Press, Oxford Univ. Press USA, 1985); *Current Protocols in Immunology* (Edited by: John E. Coligan, Ada M. Kruisbeek, David H. Margulies, Ethan M. Shevach, Warren Strober 2001 John Wiley & Sons, NY, NY); *Real-Time PCR: Current Technology and Applications*, Edited by Julie Logan, Kirstin Edwards and Nick Saunders, 2009, Caister Academic Press, Norfolk, UK; Anand, *Techniques for the Analysis of Complex Genomes*, (Academic Press, New York, 1992); Guthrie and Fink, *Guide to Yeast Genetics and Molecular Biology* (Academic Press, New York, 1991); *Oligonucleotide Synthesis* (N. Gait, Ed., 1984); *Nucleic Acid Hybridization* (B. Hames & S. Higgins, Eds., 1985); *Transcription and Translation* (B. Hames & S. Higgins, Eds., 1984); *Animal Cell Culture* (R. Freshney, Ed., 1986); *Perbal, A Practical Guide to Molecular Cloning* (1984); *Next-Generation Genome Sequencing* (Janitz, 2008 Wiley-VCH); *PCR Protocols (Methods in Molecular Biology)* (Park, Ed., 3rd Edition, 2010 Humana Press); *Immobilized Cells And Enzymes* (IRL Press, 1986); the treatise, *Methods In Enzymology* (Academic Press, Inc., N.Y.); *Gene Transfer Vectors For Mammalian Cells* (J. H. Miller and M. P. Calos eds., 1987, Cold Spring Harbor Laboratory); Harlow and Lane, *Antibodies*, (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1998); *Immunochemical Methods In Cell And Molecular Biology* (Mayer and Walker, eds., Academic Press, London, 1987); *Handbook Of Experimental Immunology*, Volumes I-IV (D. M. Weir and C C Blackwell, eds., 1986); Riott, *Essential Immunology*, 6th Edition, (Blackwell Scientific Publications, Oxford, 1988); *Embryonic Stem Cells: Methods and Protocols* (Methods in Molecular Biology) (Kurstad Turksen, Ed., 2002); *Embryonic Stem Cell Protocols: Volume I: Isolation and Characterization* (Methods in Molecular Biology) (Kurstad Turksen, Ed., 2006); *Embryonic Stem Cell Protocols: Volume II: Differentiation Models* (Methods in Molecular Biology) (Kurstad Turksen, Ed., 2006); *Human Embryonic Stem Cell Protocols* (Methods in Molecular Biology) (Kursad Turksen Ed., 2006); *Mesenchymal Stem Cells: Methods and Protocols* (Methods in Molecular Biology) (Darwin J. Prockop, Donald G. Phinney, and Bruce A. Bunnell Eds., 2008); *Hematopoietic Stem Cell Protocols* (Methods in Molecular Medicine) (Christopher A. Klug, and Craig T. Jordan Eds., 2001); *Hematopoietic Stem Cell Protocols* (Methods in Molecular Biology) (Kevin D. Bunting Ed., 2008) *Neural Stem Cells: Methods and Protocols* (Methods in Molecular Biology) (Leslie P. Weiner Ed., 2008).

Unless specific definitions are provided, the nomenclature utilized in connection with, and the laboratory procedures and

techniques of, molecular biology, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those well known and commonly used in the art. Standard techniques may be used for recombinant technology, molecular biological, microbiological, chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, and delivery, and treatment of patients.

Unless the context requires otherwise, throughout the present specification and claims, the word "comprise" and variations thereof, such as, "comprises" and "comprising" are to be construed in an open, inclusive sense, that is, as "including, but not limited to". By "consisting of" is meant including, and typically limited to, whatever follows the phrase "consisting of." By "consisting essentially of" is meant including any elements listed after the phrase, and limited to other elements that do not interfere with or contribute to the activity or action specified in the disclosure for the listed elements. Thus, the phrase "consisting essentially of" indicates that the listed elements are required or mandatory, but that no other elements are required and may or may not be present depending upon whether or not they affect the activity or action of the listed elements.

In this specification and the appended claims, the singular forms "a," "an" and "the" include plural references unless the content clearly dictates otherwise. As used herein, in particular embodiments, the terms "about" or "approximately" when preceding a numerical value indicates the value plus or minus a range of 5%, 6%, 7%, 8% or 9%. In other embodiments, the terms "about" or "approximately" when preceding a numerical value indicates the value plus or minus a range of 10%, 11%, 12%, 13% or 14%. In yet other embodiments, the terms "about" or "approximately" when preceding a numerical value indicates the value plus or minus a range of 15%, 16%, 17%, 18%, 19% or 20%.

Reference throughout this specification to "one embodiment" or "an embodiment" or "an aspect" means that a particular feature, structure or characteristic described in connection with the embodiment is included in at least one embodiment of the present invention. Thus, the appearances of the phrases "in one embodiment" or "in an embodiment" in various places throughout this specification are not necessarily all referring to the same embodiment. Furthermore, the particular features, structures, or characteristics may be combined in any suitable manner in one or more embodiments.

It should also be noted that the term "or" is generally employed in its sense including "and/or" (i.e., to mean either one, both, or any combination thereof of the alternatives) unless the content clearly dictates otherwise. The term, "at least one," for example, when referring to at least one compound or to at least one composition, has the same meaning and understanding as the term, "one or more." In addition, any ranges provided herein include all the values in the ranges.

The following examples are for illustration and are not limiting.

EXAMPLES

Example 1

Quantification of Relative T Lymphocyte DNA Representation from T Cells in Normal Tissues and from Tumor-Infiltrating T Lymphocytes in a Tumor Sample

Samples of peripheral blood, fresh adipose biopsies, frozen muscle biopsy, and skin biopsies were processed for DNA extraction using the following procedure:

Samples of 1×10^4 to 1×10^6 fresh, frozen, or fixed cells were lysed in 200 μ l of lysis buffer (50 mM TrisHCl pH7.4, 250 mM NaCl, 0.1% SDS, 0.5% Triton-X100) and 20 μ l of proteinase K (10 mg/ml) using the kitted ATL buffer and proteinase K reagents from the Qiagen Blood and Tissue kit (Qiagen #69504, Qiagen Corp., Valencia, Calif.), and incubated at 56° C. for one hour with mixing every 20 minutes. The lysate was diluted with 200 μ l of an ethanol/buffer mixture (20 mM Tris, pH 7.5, 2.0 mM EDTA, in 50% v/v ethanol) and mixed briefly. Alternatively, the AL buffer of the Qiagen Blood and Tissue kit was used. SDS precipitates formed on occasion, but were not observed to adversely impact DNA extraction or sequencing efficiency. To the diluted lysate was added 200 μ l of ethanol (96-100%).

The lysate/ethanol mixture was carefully applied to a solid support of either silica resin Sigma Celite 454 resin (Sigma #419931, Sigma, St. Louis, Mo.) or to a Qiagen Blood and Tissue kit column. The column was centrifuged at 6000 $\times g$ for one minute in a micro-centrifuge and the filtrate was discarded. The column was washed with 500 μ l of Qiagen AW1 wash buffer, or 6 M guanidine thiocyanate (GuSCN), 20 mM EDTA pH 8.0, 10 mM Tris-HCl pH 6.4, 4% Triton X-100 in 50% ethanol (v/v), and was then centrifuged at 6000 $\times g$ in a microcentrifuge for one minute. The filtrate was discarded the filtrate and the column was washed with 500 μ l of Qiagen AW2 wash buffer or 100 mM Tris, pH 7.5 in 70 ethanol (v/v), after which the column was centrifuged at 14,000 $\times g$ for three minutes, and the filtrate discarded.

Next, the column was centrifuged at 14,000 $\times g$ for one minute to dry the column of residual ethanol. 100 μ l of either Qiagen AE elution buffer, or 10 mM Tris, pH 7.5, 1 mM EDTA, was applied to the column, which was placed on a clean collection tube, incubated at room temperature for five minutes, and then centrifuged at 6000 $\times g$ for one minute to collect DNA. An aliquot of 2 μ l of the eluate was transferred to a clean tube or 96 well plate to determine yield by spectrophotometry (A_{260}/A_{280}) and the DNA concentration was calculated. An aliquot of 5 μ l of the DNA-containing eluate was transferred to a 96 well plate and diluted with 20 μ l TE for processing by qPCR.

The number of T cells in complex mixtures of tissues was estimated by determining the relative representation of T cell DNA in the samples of peripheral blood (PBMC), and in muscle, skin and adipose tissue biopsies, by quantitative PCR amplification of the rearranged TCR- β (TCRB) genes. The relative representation of T cell genomes in each tissue sample was determined by comparing the tissue sample qPCR signal profile to a calibration standard profile generated using a panel of T cell DNAs of known concentrations, and then comparing the values so obtained to the total DNA concentration of the tissue. The percent T cell composition of the tissues ranged from less than 1% in adipose tissue to greater than 92% in PBMC (Table 3).

TABLE 3

sampleID	qPCR measured T cells (nanograms)	Total DNA concentration (nanograms)	Percent T cells
SKIN_FM_6/24/11	8.25	15.31	53.9
SKIN_FMM_9/2/11	2.03	13.88	14.6
SKIN_MP_block	0.78	3.41	22.9

TABLE 3-continued

Quantitative PCR Amplification/T Cell Quantification in Tissues by Relative Representation of Adaptive Immune Receptor DNA as a Component of Tissue DNA				
sampleID	qPCR measured T cells (nanograms)	Total DNA concentration (nanograms)	Percent T cells	
SKIN_RB_8/11/11	7.43	14.85	50.0	
SKIN_RB_9/8/11	2.46	18.46	13.3	
SKIN_TB_7/13/11	1.52	19.95	7.6	
MUSCLE_1995_-2-6	0.13	3.06	4.32	
MUSCLE_1995_-8-	0.05	2.24	2.23	
MUSCLE_2062_-2-6	4.18	6.62	63.18	12
MUSCLE_2062_-8-	2.20	8.02	27.47	12
MUSCLE_2417_-2-6	0.47	4.94	9.50	12
MUSCLE_2417_-8-	0.07	4.64	1.47	12
MUSCLE_2426_-2-6	0.17	4.35	4.02	20
MUSCLE_2426_-8-	0.21	6.31	3.34	12
MUSCLE_2444_-2-6	0.02	3.29	0.68	12
MUSCLE_2444_-8-	0.16	13.79	1.19	12
MUSCLE_2450_-2-6	2.33	4.42	52.78	25
MUSCLE_2450_-8-	1.51	5.22	28.90	12
PBMC_9	15.52	90.55	17.14	
PBMC_8	87.59	124.32	70.45	
PBMC_7	10.42	42.97	24.26	
PBMC_6	115.52	125.33	92.17	
PBMC_5	21.15	46.09	45.88	30
PBMC_4	36.35	130.00	27.96	
PBMC_3	10.81	142.16	7.60	
PBMC_14	11.14	49.08	22.70	
PBMC_11	94.22	223.56	42.14	
ADIPOSE_8-SQ	0.50	10.55	4.70	
ADIPOSE_8-OM	1.90	19.34	9.84	
ADIPOSE_6-SQ	0.43	11.22	3.80	
ADIPOSE_6-OM	0.64	19.14	3.35	
ADIPOSE_4-SQ	0.20	8.22	2.39	
ADIPOSE_4-OM	3.49	34.23	10.21	
ADIPOSE_2-SQ	0.83	11.62	7.14	
ADIPOSE_2-OM	1.00	18.39	5.44	
ADIPOSE_17-SQ	2.44	11.59	21.10	40
ADIPOSE_17-OM	0.24	18.94	1.27	
ADIPOSE_16-SQ	0.72	6.13	11.79	
ADIPOSE_16-OM	0.96	33.66	2.85	
ADIPOSE_14-SQ	0.23	8.97	2.56	
ADIPOSE_14-OM	1.60	10.57	15.13	
ADIPOSE_11-SQ	0.60	9.67	6.22	45
ADIPOSE_11-OM	0.06	60.21	0.10	
ADIPOSE_10-SQ	2.50	11.51	21.70	
ADIPOSE_10-OM	0.63	105.50	0.60	

Example 2

Quantification of Tumor-Infiltrating T Lymphocytes in a Tumor Sample Using a TCR β V-Region Specific qPCR Probe

55

Tumor-infiltrating T lymphocytes (TILs) were quantified using a multiplex real-time PCR assay as follows.

Multiplex Primer Sequences:

The multiplex oligonucleotide primer sets that were used had the sequences shown in Table 1. The "r" in Table 1B represents a ribonucleotide base in the oligonucleotide sequence and "/3SpC3/" represents a 3' three carbon spacer on the hydroxyl group preventing polymerase extension and amplification. The DNA repair endonuclease cleaves the oligonucleotide at the ribonucleotide after hybridization to a complementary sequence, creating an unblocked hydroxyl group that can be extended by a polymerase.

60

65

Assay Reagents: 20 μ l PCR reactions were set up having final concentrations of 1 \times Taq polymerase buffer, 10 ng/ μ l analyte DNA, 1 micromolar TCRBV_RN2 oligonucleotide primer mix (Table 1), 1 micromolar TCRBJ_RN2 oligonucleotide primer mix (Table 1), and 0.1 milliunits/ μ l of RNase H2 (IDT, Coralville, Iowa). Analytes and standard PCR reactions were set up in quadruplicate.

Thermal Cycling Conditions: Reactions were thermal cycled on a real time PCR platform (ILLUMINA ECO™, Illumina Inc., San Diego, Calif.) with the amplification profile of 95° C. for 5 minutes, followed by 80 cycles of incubations at 95° C. for 15 seconds, 58° C. for 30 seconds. Following thermocycling, a melt curve was collected at 55° C. for 15 seconds.

Standards (See Table 4.) Purified T cell DNA was extracted from TCR $\alpha\beta$ -positive bead-sorted peripheral blood cells (Miltenyi 130-091-236), then serially diluted and used in the thermal cycling reaction conditions as described above at concentrations ranging from 60 picograms to 250 nanograms per reaction.

Data Analysis: A standard curve was calculated for each replicate of the DNA standards and evaluated for consistency by calculating the r^2 . The Ct was determined for each replicate of the analytes, then averaged and evaluated for consistency by calculating the standard deviation. The average T cell concentration of each analyte was determined by extrapolating from the standard curve using the Cq for each replicate. In particular, in order to measure the number of TCR genomes, it was assumed that there was 3 pg DNA/cell. Once the amount of starting DNA was calculated using real-time qPCR with the standards as described in Table 4, it was possible to calculate the number of TCR genomes in the sample.

FIG. 1A shows a sample output from a TIL qPCR experiment demonstrating the amplification profile of standard T cell DNA (shown as gray traces in the Amplification plot) and TIL samples (shown as black traces) as measured by the RFU (relative fluorescent units) of SYBR™ green incorporated in the amplification products. T cell sample DNA was obtained from peripheral blood and tissues by purification on a silica matrix (Qiagen 69504). The Ct values of the standards, calculated from the cycle at which the standard DNA amplification profile reached the threshold of exponential amplification (indicated by the horizontal line), were fitted to a standard curve (FIG. 1B) which was used to extrapolate the concentration of T cells in the complex mixtures of peripheral blood DNA. The Cq values were determined for the standards of known DNA concentrations, measured in four replicate amplifications, and are shown as circles in the standard curve plot (FIG. 1B). The T cell DNA concentrations of the peripheral blood and tissue (tumor) samples, indicated by Xs, were determined from the best fit of the log of the standard DNA concentration plotted against standard DNA Cq value.

The DNA concentration of T cell genomes in a complex mixture of solid tumor DNA was thus measured by comparing the Ct value from the sample to the Ct values obtained from known quantities of purified T cell DNA. The Ct values of the standards were obtained from the amplification plot and were then used to prepare the standard curve from which the corresponding T cell concentration was determined for the tumor DNA samples (Table 4).

TABLE 4

TILs Quantified by Relative Representation of Rearranged TCR β Encoding DNA in Tumor DNA Sample				
			TCRB starting conc. (ng/ μ l)	Average estimated T cell DNA concen. (ng/ μ l)
10	LZ-INF1-tet-	A	45.19	1.13E+02
	LZ-INF1-tet-	B	43.18	5.93E+02
	LZ-INF1-tet-	C	44.46	2.08E+02
	LZ-INF1-tet-	D	45.7	7.49E+01
	LZ-INF1-tet+	A	48.34	8.54E+00
	LZ-INF1-tet+	B	48.27	9.08E+00
	LZ-INF1-tet+	C	49.13	4.45E+00
	LZ-INF1-tet+	D	49.89	2.39E+00
	LZ-INF2-D+30	A	47.3	2.00E+01
	LZ-INF2-D+30	B	46.4	4.21E+01
15	LZ-INF2-D+30	C	45.53	8.62E+01
	LZ-INF2-D+30	D	47.77	1.36E+01
	LZ-INF2-tet-	A	45.67	7.69E+01
	LZ-INF2-tet-	B	44.06	2.87E+02
	LZ-INF2-tet-	C	44.09	2.81E+02
	LZ-INF2-tet-	D	43.56	4.34E+02
	LZ-INF2-tet+	A	48.53	7.34E+00
	LZ-INF2-tet+	B	47.09	2.39E+01
	LZ-INF2-tet+	C	48.88	5.50E+00
	LZ-INF2-tet+	D	47.79	1.34E+01
20	GV-INF1-D+508	A	46.4	4.20E+01
	GV-INF1-D+508	B	44	3.01E+02
	GV-INF1-D+508	C	45.22	1.11E+02
	GV-INF1-D+508	D	44.18	2.61E+02
				269.72
				40.48
				12.53
				178.75
25				

The presently described method provided a quantitative and highly sensitive method for enumerating T or B cell genomes in samples where such analysis was previously not possible, such as formalin fixed or frozen samples. The present methods were sensitive enough to detect as low as picogram quantities of T or B cell genomes (e.g. fewer than 100 T or B cells in a complex mixture of non-T or non-B cells, such as a solid tumor).

TABLE 5

T cell standards				
	Standard	Standard conc. (ng/ μ l)	Amount amplified (ng)	T cell genomes amplified
40	1	50	250	83333
	2	12.50	62.50	20833
	3	3.13	15.63	5208
	4	0.78	3.91	1302
	5	0.20	0.98	326
	6	0.05	0.24	81
	7	0.01	0.06	20
	8	0	0	0

Example 3

Quantification of Tumor-Infiltrating T Lymphocytes in a Tumor Sample Using a V7-Specific qPCR Probe

TCRB V7+ tumor-infiltrating T lymphocytes are quantified using a multiplex real-time PCR assay as follows.

Multiplex Primer Sequences: The multiplex primer sequences are provided in Table 1. The “r” represents a ribonucleotide base in the oligonucleotide sequence and “/3SpC3/” represents a 3' three carbon spacer on the hydroxyl group preventing polymerase extension and amplification. The DNA repair endonuclease cleaves the oligonucleotide at

65

the ribonucleotide after hybridization to a complementary sequence, creating an unblocked hydroxyl group that can be extended by a polymerase.

Assay Reagents (Volumes and Concentrations): The assay consists of a 20 µl PCR reaction at final concentrations of 1× Taq polymerase buffer, 10 ng/µl analyte DNA, 1 micromolar TCRBV_RN2 oligonucleotide primer mix, 1 micromolar TCRBJ_RN2 oligonucleotide primer mix) 100 nanomolar TAQMANT™ probe (SEQ ID NO:66), 0.1 milliunits/µl of RNase H2 (IDT). Analytes and standard PCR reactions are set up in quadruplicate.

Thermal Cycling Conditions: Reactions are thermal cycled on a real time PCR platform (such as the ILLUMINA ECO™ or Bio Rad CFX384) with the amplification profile of 95° C. for 5 minutes, followed by 80 cycles of incubations at 95° C. for 15 seconds, 58° C. for 30 seconds. Following thermocycling, a melt curve is collected at 55° C. for 15 seconds.

Standards (See Table 5.) Purified T cell DNA is extracted from TCRαβ positive bead-sorted peripheral blood cells (Miltenyi 130-091-236), then serially diluted and used in the thermal cycling reactions as described above at concentrations ranging from 60 picograms to 250 nanograms per reaction.

Data Analysis: A standard curve is calculated for each replicate of the DNA standards and evaluated for consistency by calculating the r^2 . The cycle threshold, Ct, is determined for each replicate of the analytes, then averaged and evaluated for consistency by calculating the standard deviation. The average T cell concentration of each analyte is determined by extrapolating from the standard curve using the Cq for each replicate. In particular, in order to measure the number of V7+ TCR genomes, it is assumed that there is 3 pg DNA/cell. Once the amount of starting DNA is calculating using real-time qPCR with the standards as described in Table 2A, it is possible to calculate the number of TCR genomes in the sample.

The present Example demonstrates the quantitative and highly sensitive method for enumerating TCRB V7+ T cells in a mixed population of cells.

Example 4

Quantification of TCRB V18+ and TCBV19+ Tumor-Infiltrating T Lymphocytes in a Buffy Coat Sample Using dPCR

TCRB V18+ and V19+ tumor-infiltrating T lymphocytes were quantified in a buffy coat sample using a digital PCR (dPCR) assay as described herein, with RNase P as an internal control as follows.

Equipment:

QX100 Droplet Digital PCR System (Bio-rad, Item No. 186-3001)

Heat Sealer (Eppendorf, Item No. 951023078)

Primer and Probe Sequences: The following primers and probes were used for the dPCR assay:

V Region (Forward) Primers

V18-specific:

ATTTCTGCTGAATTCCCAAAGAGGGCC (SEQ ID NO: 686)

V19-specific:

(SEQ ID NO: 843, have TATA 5' upstream of TRBV19 SEQ ID NO: 656)

TATAGCTGAAGGGTACAGCGTCTCTCGGG (SEQ ID NO: 656)

66

J Region (Reverse) Primers

		(SEQ ID NO: 696)
5	J1-1	TTACCTACAACGTGAGTCTGGTGCCTTGTCAAA
		(SEQ ID NO: 880)
	J1-2	ACCTACAACGGTTAACCTGGTCCCCGAACCGAA
		(SEQ ID NO: 881)
	J1-3	ACCTACAACAGTGAGCCAACCTCCCTCTCCAAA
		(SEQ ID NO: 882)
	J1-4	CCAAGACAGAGAGCTGGGTTCCACTGCCAAA
		(SEQ ID NO: 700)
	J1-5	ACCTAGGATGGAGAGTCGAGTCCCACCAACAA
		(SEQ ID NO: 883)
	J1-6	CTGTCACAGTGAGCCTGGTCCCCTGGCCAAA
		(SEQ ID NO: 702)
	J2-1	CGGTGAGCCGTGTCCTGGCCCGAA
		(SEQ ID NO: 703)
	J2-2	CCAGTACGGTCAGCCTAGAGCCTCTCCAAA
		(SEQ ID NO: 704)
	J2-3	ACTGTCAGCCGGGTGCCTGGGCCAAA
		(SEQ ID NO: 705)
	J2-4	AGAGCCGGTCCGGCGCCGAA
		(SEQ ID NO: 706)
	J2-5	GGAGCCGCGTGCCTGGCCCGAA
		(SEQ ID NO: 707)
	J2-6	GTCAGCCTGCTGCCGGCCCCGAA
		(SEQ ID NO: 708)
	J2-7	GTGAGCCTGGTGCCTGGCCCGAA

TCRB V Region Probes

V18-specific:	FAM-ATCCAGCAGTAGTGCAGG-MGB	(SEQ ID NO: 796)
V19-specific:	FAM-CACTGTGACATCGGCCAA-MGB	(SEQ ID NO: 797)

RNaseP Primers and Probe

RNaseP forward primer:	AGATTTGGACCTGCGAGC	(SEQ ID NO: 840)
RNaseP reverse primer:	GAGCGGCTGTCTCACAAAGT	(SEQ ID NO: 841)
RNaseP-VIC probe:	CCGCGCAGAGCTTC	(SEQ ID NO: 842)

Assay Reagents:

The reaction mixture contained 900 nM V18-specific forward primer (or V19-specific forward primer), 900 nM each of the 13 J region reverse primers, 900 nM RNaseP forward primer, 900 nM RNaseP reverse primer, 250 nM V18-specific TAQMANT™ probe (or V19-specific probe) with FAM fluorophore, 900 nM RNaseP probe with VIC fluorophore, 0-100 ng sample DNA, and ddPCR supermix (Catalogue No. 186-3027 from Bio-RAD, Hercules, USA). Bulk reaction volumes were converted into 1 nL droplet-in-oil immersions with the QX100 ddPCR System Droplet Generator (Bio-Rad) via the standard vendor's protocol. Droplets were cycled with the following conditions: 95° C. for 10 min, followed by 50 cycles of 94° C. for 30 sec and 61° C. for 1 min, then held at 10° C. Droplets were individually analyzed for fluorescence

67

by flow cytometry in the QX100 ddPCR System Droplet Reader (Bio-Rad) according to the manufacturer's instructions. A threshold was set between highly fluorescent droplets (containing target molecules) and less fluorescent droplets (without target molecules), and the concentrations of target molecules were calculated by Poisson statistics to quantify T cells (FAM) and total cells (VIC) in each well.

Data Analysis:

The data were analyzed using QUANTASOFT™ software. QUANTASOFT™ calculated FAM and VIC concentration values for each well. Fluorescence thresholds were set so that they were above the negative droplets and below the positive droplets.

The data can be reported in two different ways. The first reports the ratio of genomes with rearranged TCRB genes to total diploid genomes. This ratio is computed by dividing the number of molecules with a TCRB rearrangement, as determined by PCR amplification and V specific probes, by half the number of RNaseP genes, as determined by PCR amplification and RNaseP specific probes. The factor of a half is required because each diploid genome has two RNaseP genes. Data reported in this manner are described in this example.

Alternatively, a second set of data can be reported. This is output as an estimation of the fraction of T cells in a sample. Approximately 80% of $\alpha\beta$ T cells have only one of their two TCR β alleles rearranged. The other 20% have both alleles rearranged, with one of the two being productively rearranged and the other non-productively rearranged. Other cell types lack the TCR β rearrangement. Hence, an accurate count of the number of TCR β rearrangements in a sample of cells is directly proportional to the number of T cells within that mix.

68

To approximate the number of T cells in the sample, the total count of TCRB rearrangements is divided by 1.2. So, this second data analysis is equal to the first count described above divided by 1.2.

FIG. 3 shows a sample output from a TIL dPCR experiment using buffy coat DNA as the template. Each data point represents a single dPCR specific reaction for the V18, V19 or RNaseP gene segment. Droplets were assigned as positive or negative based on their fluorescence amplitudes. The number of positive and negative droplets in each channel was used to calculate the concentration of target molecules and the Poisson-based confidence intervals to enumerate the V gene segment-specific T lymphocyte population. In this sample, 0.6% of the sample was composed of V18-specific T lymphocytes, while 1.2% of the sample was V19-specific T lymphocytes.

Example 5

dPCR-Based Detection of Tumor-Infiltrating Lymphocytes

Tumor-infiltrating T lymphocytes were quantified by detecting rearranged DNA encoding TCRB using a digital droplet PCR (dPCR) assay with the RNase P gene as an internal control as follows.

Equipment:

QX100 Droplet Digital PCR System (Bio-rad, Item No. 186-3001)

Heat Sealer (Eppendorf, Item No. 951023078)

Primer and Probe Sequences: The following primers and probes were used for the dPCR assay:

V Region (Forward) Primers

No.	Name	Sequence (5' to 3')	SEQ ID NO.
1	V02	TTC GAT GAT CAA TTC TCA GTT GAA AGG CC	844
2	V03-1	CCT AAA TCT CCA GAC AAA GCT CAC TTA AA	845
3	V04-1	CTG AAT GCC CCA ACA GCT CTC TCT TAA AC	846
4	V04-2/3	CTG AAT GCC CCA ACA GCT CTC ACT TAT TC	847
5	V05-1	TGG TCG ATT CTC AGG GCG CCA GTT CTC TA	848
6	V05-3	TAA TCG ATT CTC AGG GCG CCA GTT CCA TG	849
7	V05-4	TCC TAG ATT CTC AGG TCT CCA GTT CCC TA	850
8	V05-5	AAG AGG AAA CTT CCC TGA TCG ATT CTC AGC	694
9	V05-6	GGC AAC TTC CCT GAT CGA TTC TCA GGT CA	851
10	V05-8	GGA AAC TTC CCT CCT AGA TTT TCA GGT CG	852
11	V06-1	GTC CCC AAT GGC TAC AAT GTC TCC AGA TT	661
12	V06-2/3	GCC AAA GGA GAG GTC CCT GAT GGC TAC AA	853
13	V06-4	GTC CCT GAT GGT TAT AGT GTC TCC AGA GC	854
14	V06-5	AAG GAG AAG TCC CCA ATG GCT ACA ATG TC	693
15	V06-6	GAC AAA GGA GAA GTC CCG AAT GGC TAC AAC	675
16	V06-7	GTT CCC AAT GGC TAC AAT GTC TCC AGA TC	855
17	V06-8	CTC TAG ATT AAA CAC AGA GGA TTT CCC AC	856
18	V06-9	AAG GAG AAG TCC CCG ATG GCT ACA ATG TA	692

-continued

No.	Name	Sequence (5' to 3')	SEQ ID NO.
19	V07-1	TCC CCG TGA TCG GTT CTC TGC ACA GAG GT	857
20	V07-2	AGT GAT CGC TTC TCT GCA GAG AGG ACT GG	858
21	V07-3	GGC TGC CCA ACG ATC GGT TCT TTG CAG T	859
22	V07-4	GGC GGC CCA GTG GTC GGT TOT CTG CAG AG	860
23	V07-6/7	ATG ATC GGT TCT CTG CAG AGA GGC CTG AGG	861
24	V07-8	GCT GCC CAG TGA TCG CTT CTT TGC AGA AA	862
25	V07-9	GGT TCT CTG CAG AGA GGC CTA AGG GAT CT	863
26	V09	GTT CCC TGA CTT GCA CTC TGA ACT AAA C	864
27	V10-1	AAC AAA GGA GAA GTC TCA GAT GGC TAC AG	865
28	V10-2	GAT AAA GGA GAA GTC CCC GAT GGC TAT GT	866
29	V10-3	GAC AAA GGA GAA GTC TCA GAT GGC TAT AG	867
30	V11-1/2/3	CTA AGG ATC GAT TTT CTG CAG AGA GGC TC	868
31	V12-3/4	TCG ATT CTC AGC TAA GAT GCC TAA TGC	869
32	V12-5	TTC TCA GCA GAG ATG CCT GAT GCA ACT TTA	870
33	V13	CTG ATC GAT TCT CAG CTC AAC AGT TCA GT	871
34	V14	TCT TAG CTG AAA GGA CTG GAG GGA CGT AT	650
35	V15	GCC GAA CAC TTC TTT CTG CTT TCT TGA C	872
36	V16	TTC AGC TAA GTG CCT CCC AAA TTC ACC CT	873
37	V18	ATT TTC TGC TGA ATT TCC CAA AGA GGG CC	686
38	V19	TAT AGC TGA AGG GTA CAG CGT CTC TCG GG	874
39	V20-1	ATG CAA GCC TGA CCT TGT CCA CTC TGA CA	875
40	V24-1	ATC TCT GAT GGA TAC AGT GTC TCT CGA CA	876
41	V25-1	TTT CCT CTG AGT CAA CAG TCT CCA GAA TA	877
42	V27	TCC TGA AGG GTA CAA AGT CTC TCG AAA AG	878
43	V28	TCC TGA GGG GTA CAG TGT CTC TAG AGA GA	652
44	V29-1	CAT CAG CCG CCC AAA CCT AAC ATT CTC AA	685
45	V30	GAC CCC AGG ACC GGC AGT TCA TCC TGA GT	879

50

J Region (Reverse) Primers

The J region reverse primers were the same as in Example

-continued

No.	Name	Specific to	Sequence (5' to 3')	SEQ ID NO.
4.	TCRB V Region Probes			
	All probes included a minor groove binder (MGB) and had a FAM fluorophore on the 5' end.	55		
1	V02	V02	TCCGGTCCACAAAGCTGGAG	908
2	V03	V03-1, V03-2p	CTGGAGCTTGGTGACTCTGC	909
3	V04a	V04-1	TCACCTACACGCCCTGC	835
				60
			4 V04b V04-2, V04-3	ACACACCCTGCAGCCAG
			5 V05a1 V05-1	AGCACCTTGGAGCTGG
			6 V05a2 V05-3	TGAGTGCCTTGGAGCTGG
			7 V05b V05-4, V05-5, V05-6, V05-7, V05-8	TGAGCTGAATGTGAACGCCTT
			65	

71

-continued

No.	Name	Specific to	Sequence (5' to 3')	SEQ ID NO.
8	V06a	V06-1, V06-2, V06-3	TGGAGTCGGCTGCTCC	809
9	V06b	V06-7, V06-9	CTGGAGTCAGCTGCTCCC	823
10	V06c	V06-4	CACAGATGATTCCCCCTC	837
11	V06d	V06-1, V06-5, V06-6, V06-8, V06-9	TGCTCCCTCCAGACATC	811
12	V07a1	V07-1	CTGAAGTTCCAGCGCACA	838
13	V07a2	V07-2	TCCGTCTCCACTCTGACGA	839
14	V07b	V07-3, V07-4, V07-8	ACTCTGAAGATCCAGCGCA	824
15	V07c	V07-4, V07-6, V07-9	TCCAGCGCACAGAGCA	828
16	V07d	V07-7	CAGCGGGACTCAGCCA	829
17	V09	V09	TGAGCTCTGGAGCTGG	815
18	V10a1	V10-1	TCAAACACAGAGGACCTCCC	830
19	V10a2	V10-2	CACTCTGGAGTCAGCTACCC	831
20	V10b	V10-3	TCACACTGGAGTCCGCTACC	787
21	V11	V11-1, V11-2, V11-3	AGTAGACTCCACTCTCAAGATCCA	788
22	V12c	V12-3, V12-4, V12-5	ATCCAGCCCTCAGAACCCAG	791
23	V13	V13	ACATGAGCTCCTGGAGCTG	792
24	V14	V14	TGCAGAACTGGAGGATTCTGG	793
25	V15	V15	TGTACCTGTGTGCCACCAGC	794
26	V16	V16	CCTTGAGATCCAGGCTACG	816
27	V18	V18	ATCCAGCAGGTAGTGCAGG	796
28	V19	V19	CACTGTGACATCGGCCCCAA	797
29	V20	V20-1	CAGTCCCCATCCTGAAGACA	798
30	V24	V24-1	TGTCCCTAGAGTCTGCCATCC	800
31	V25	V25-1	CAGGCCCTCACATACCTCTC	801
32	V27	V27-1	TGGAGTCGCCCCAGCC	818
33	V28	V28	AGGAGCGCTTCTCCCTG	819
34	V29	V29-1	TGTGAGCAACATGAGCCCTG	804
35	V30	V30	TCCTTCTCAGTGAECTGGC	820

RNaseP Primers and Probe

The RNase P primers and probe were the same as in Example 4.

72

Assay Reagents:

The assay reagents were prepared as follows:

V Region Primer/Probe Mix

The V region (forward) primers and Taqman probes were assigned to 8 different subgroups (A through H). Each subgroup contained 3 to 4 probes and 4 to 7 corresponding primers, allowing each subgroup to specifically detect a subset of T-cell rearrangements. The subgroups were as follows:

Subgroup	Probes	Primers
A	V02	V02
	V14	V14
	V15	V15
	V29	V29-1
B	V05a1	V05-1
	V06a	V06-1
		V06-2
		V06-3
C	V13	V13
	V28	V28
	V05b	V05-4
		V05-5
D		V05-6
		V05-7
		V05-8
	V09	V09
E	V25	V25-1
	V27	V27-1
	V06b	V06-7
		V06-9
F	V06d	V06-1
		V06-5
		V06-6
		V06-8
G		(V06-9)
	V18	V18
	V20	V20-1
	V05a2	V05-3
H	V12c	V12-3
		V12-4
		V12-5
	V24	V24-1
I	V30	V30
	V07c	V07-4
		V07-6
		V07-9
J	V07d	V07-7
	V10a1	V10-1
	V10a2	V10-2
	V11	V11-1
K		V11-2
		V11-3
	V16	V16
	V19	V19
L	V03	V03-1
	V07b	V07-3
		V07-4
		V07-8
M	V10b	V10-3

Although eight subgroups (A-H) were prepared as described herein with subsets of primers and probes, other embodiments are contemplated in which all probes and primers may be present in a single reaction or in 7, 6, 5, 4, 3 or 2 reactions, or alternatively in a greater number of reactions, where the number of reactions may vary as a function of herein described parameters that may be altered for particular assay configurations, such as concentrations of the assay components, amplification cycle steps, instrumentation capacity and capabilities, and other factors. For each subgroup described in this example, a 20 \times stock mix was made. Primer concentrations were 18 μ M each in the stock, and 900 nM in the final reaction volume. Probe concentrations were 5 μ M each in the stock, and 250 nM in the final reaction volume.

73

For example, a recipe for a 20x stock of the subgroup A primer/probe mix was as follows:

	Volume added (μL)
V02 forward primer (1000 μM)	3.6
V14 forward primer (1000 μM)	3.6
V15 forward primer (1000 μM)	3.6
V29-1 forward primer (1000 μM)	3.6
V02-FAM Taqman probe (1000 μM)	10
V14-FAM Taqman probe (1000 μM)	10
V15-FAM Taqman probe (1000 μM)	10
V29-FAM Taqman probe (1000 μM)	10
Nuclease-free water	145.6
Total	200

J Region Primer Mix

All 13 J region (reverse) primers were combined into a 20x stock. Primer concentrations were 18 μM each in the stock, and 900 nM in the final reaction volume. The recipe was as follows:

	Volume added (μL)
J1-1 reverse primer (1000 μM)	3.6
J1-2 reverse primer (1000 μM)	3.6
J1-3 reverse primer (1000 μM)	3.6
J1-4 reverse primer (1000 μM)	3.6
J1-5 reverse primer (1000 μM)	3.6
J1-6 reverse primer (1000 μM)	3.6
J2-1 reverse primer (1000 μM)	3.6
J2-2 reverse primer (1000 μM)	3.6
J2-3 reverse primer (1000 μM)	3.6
J2-4 reverse primer (1000 μM)	3.6
J2-5 reverse primer (1000 μM)	3.6
J2-6 reverse primer (1000 μM)	3.6
J2-7 reverse primer (1000 μM)	3.6
Nuclease-free water	153.2
Total	200

RNaseP Reference Assay Mix

RNaseP was used as a reference gene to quantify the number of cells interrogated. The RNaseP gene was known to be present at two copies per diploid genome.

The 20x RNaseP reference assay stock was prepared as follows:

	Volume added (μL)
RNaseP forward primer (100 μM)	36
RNaseP reverse primer (100 μM)	36
RNaseP-VIC Taqman probe (100 μM)	36
Nuclease-free water	92
Total	200

Bulk dPCR Volumes

Before droplet generation, bulk dPCR volumes were prepared. A plate of bulk dPCRs was prepared with each well having the following recipe:

Reagent	1X
dPCR Supermix (2X)	12.5 μL
V primer/probe mix (20X)	1.25 μL
J primer mix (20X)	1.25 μL
RNaseP reference mix (20X)	1.25 μL

74

-continued

Reagent	1X
DNA (20 ng/μL)	5 μL
Nuclease-free water	3.75 μL

Total	25 μL
-------	-------

A typical plate was configured as shown in FIG. 4. Samples 10 through 10 were the experimental samples. The negative control was genomic DNA from a source where no detection of T-cell rearrangements was expected (e.g., HT29 human colon adenocarcinoma cells, a non-lymphoid cancer cell line, catalogue number HTB-38™, American Type Culture Collection, Manassas, Va.), and the “no template control” (NTC) group used water in the place of DNA.

1) To set-up the plate, primary mastermix was created:

Reagent	1X	106X
dPCR Supermix (2X)	12.5 μL	1325 μL
V primer/probe mix (20X)	1.25 μL	—
J primer mix (20X)	1.25 μL	132.5 μL
RNaseP reference mix (20X)	1.25 μL	132.5 μL
DNA (20 ng/1L)	5 μL	—
Nuclease-free water	3.75 μL	397.5 μL

Total	25 μL	1987.5 μL
-------	-------	-----------

2) Then individual mastermixes for each assay subgroup were created:

Reagent	13X
Primary mastermix (see above)	243.75
V primer/probe mix (20X)	16.25
Total	260 μL

3) Each subgroup mastermix was pipetted into all appropriate wells, and then the sample DNA (or water for NTC wells) was pipetted in each well of the indicated column:

Reagent	1X
Subgroup mastermix	20 μL
DNA (20 ng/μL)	5 μL

Total (final)	25 μL
---------------	-------

4) The plate was sealed with a removable foil PCR sheet and briefly spun in a centrifuge (e.g., 1000×g for 5 seconds) to make sure the dPCR bulk reaction volumes were at the bottom of each well.

Droplet Generation:

Wells of a DG8 cartridge were each loaded with 20 μL of reaction mixture. Droplets were generated and transferred 60 into a fresh Eppendorf twin.tec PCR plate (Eppendorf, Order No. 0030 128.648). The plate was then heat-sealed.

Thermal Cycling Conditions:

The thermal cycling conditions were the same as described above in Example 4.

65 Data Analysis:

The data were analyzed using QUANTASOFT™ software (Bio-Rad, Hercules, Calif.). QUANTASOFT™ calculated

FAM and VIC concentration values for each well. Fluorescence thresholds were set so that they were above the negative droplets and below the positive droplets. To determine the fraction of cells with TCRs of a given subgroup in a given well, the following formula was used:

$$\text{Fraction of Cells with TCRs(subgroup } X\text{)} = \frac{2 * (\text{FAM concentration})}{(\text{VIC concentration})}$$

The above formula was applied to a sample data set to determine % TIL and the results were as follows:

Subgroup	FAM concentration (TCRs)	VIC concentration (RNaseP)	Fraction of Cells with TCRs from Subgroup
A	16.3	728	0.04
B	30.5	810	0.08
C	27.9	708	0.08
D	36.9	690	0.11
E	30.6	741	0.08
F	34.4	782	0.09
G	17.9	735	0.05
H	13.8	715	0.04
Total fraction of cells with TCRs =			0.56

Example 6

dPCR-Based Detection and Characterization of Tumor-Infiltrating Lymphocytes in a Leukemia Patient

Digital PCR reactions in this example were performed essentially as described above in Examples 4 and 5. In pilot studies, subgroups A-H mastermixes were processed for thermal cycling as described above using template DNA (20 ng/ μ L) from either isolated human peripheral blood T cells of a healthy donor or from HT29 cells, or no-template controls (NTC), with FAM signal for TCR and VIC for the internal control RNase P gene as described above. FIG. 5A shows representative data for the eight subgroups, in which pronounced detection of amplification products can be seen when T cell DNA templates were present, with virtually no background signal detectable when non-lymphoid HT29 DNA was used as the template, or when no template was present (NTC). Each data point represents a single dPCR specific reaction for the probes of subgroups A through H. Droplets are assigned as positive (above horizontal separation lines) or negative (below horizontal separation lines) based on their fluorescence amplitudes. The number of positive and negative droplets in each channel was used to calculate the concentration of target molecules and the Poisson-based confidence intervals to enumerate the V gene segment-specific T lymphocyte population.

Tumor-infiltrating T lymphocytes in a sample from a patient with T cell acute lymphocytic leukemia (T-ALL) were quantified using a dPCR assay with the RNase P gene as an internal control, essentially as described above according to Example 5. For use as amplification template, DNA was extracted from a bone marrow sample taken prior to treatment of the patient. The results of dPCR using 8 different subgroups of probes and primers (A through H) and DNA from the sample are shown in FIG. 5B. Each data point represents a single dPCR specific reaction for the probes of subgroups A through H. Droplets are assigned as positive (above horizontal separation lines) or negative (below horizontal separation lines) based on their fluorescence amplitudes. The number of

positive and negative droplets in each channel was used to calculate the concentration of target molecules and the Poisson-based confidence intervals to enumerate the V gene segment-specific T lymphocyte population. The results showed that a majority (79.7%) of the cells from the sample of the patient had the rearranged V β segment(s) of subgroup A. Similar evidence of clonal overrepresentation within a subgroup was also independently observed when template DNA from another T-ALL patient was analyzed in the dPCR assay for quantifying T cells in the sample by TCRB rearrangement; in that patient a pronounced signal representing >90% of cells was detected in subgroup B. By contrast, when template DNA from a patient diagnosed with early thymic precursor (ETP) T-ALL was used in the dPCR method, substantially no rearranged TCRB FAM signal was detectable, consistent with TCR gene rearrangement not having yet taken place in ETP cells that occur as the predominant clonal population in ETP T-ALL (FIG. 5C).

Example 7

Preferential Use of Different V β Gene Segments by CD4+ and CD8+ Cells

For each V β segment, the frequency is calculated with which productively rearranged TCR sequences in each of the CD4+ samples are used (CD4+ and CD8+ T cell populations were sorted using a FacsARIA, BD Biosciences, San Jose, Calif.), and the mean value of these frequencies is taken to be the population mean usage for that V β segment. This value is compared to the usage of each segment in CD8+ T cells. Many of the individual V β segments are preferentially used more frequently in either CD4+ cells relative to their usage in CD8+ cells, or in CD8+ cells relative to their usage in CD4+ cells. To assess statistical significance of such preferential usage, a two-tailed unpaired t-test for difference of means is performed. 21 of 48 measured V β segments have differential usage between CD4+ and CD8+ samples, indicating that T cell subpopulation differentiative pathways influence the frequency with which TCR gene rearrangements bearing certain particular V gene segments survive the selection process.

Having established the existence of TCR sequence features that distinguish CD4+ from CD8+ T cells, a computational method was developed to estimate the proportion of T cells that are CD4+ in an unknown sample using TCR sequence data alone. Briefly, a usage frequency for each V β segment was calculated for CD4+ and CD8+ T cells using flow-sorted samples from 42 subjects. These values were used to train a likelihood model which treats each observed TCR sequence as independent and uses the observed means as generative probabilities.

To determine the likelihood of new data under this model, a proportion of CD4+ T cells, p, is assumed. The observed mean usage for each V β segment in the training data for CD4+ T cells is taken to be the same as the probability of an unknown CD4+ T cell using that segment, and likewise for CD8+ T cells. Thus, the likelihood of observing in new data a single sequence with a given V β segment is calculated as:

$$[p * P(V|CD4)] + [(1-p) * P(V|CD8)]$$

The likelihood of a dataset is calculated as the product of the likelihoods of its constituent sequences. To determine the proportion of CD4+ T cells in new data, the likelihood of the new data is calculated at each p from 0 to 1 with a granularity of 0.01, and the value of p leading to the highest likelihood of the observed data is chosen as the estimate of the proportion of CD4+ T cells in the sample.

77
Example 8

dPCR-Based Detection and Clonality Analysis of
Tumor-Infiltrating Lymphocytes in Cervical Tumor
Biopsies

This example describes quantitative digital droplet PCR quantification of TIL in three fresh-frozen solid human ovarian tumor samples obtained from distinct sites of the same tumor from the same cervical cancer patient. Genomic DNA was extracted from tumor punch biopsies using a proteinase K digest and solid-phase reversible immobilization, magnetic bead technology (Agencourt #A41497) on a BIOMEK™ FX workstation according to the manufacturers' instructions. Following extraction, the DNA yield and purity were assessed using UV spectral analysis on a TRINEAN DROPSENSE™ spectrophotometer by measuring the UV absorbance at 260 nm (A_{260}) and 280 nm (A_{280}). DNA samples were then processed for quantitative digital droplet PCR. Tumor-infiltrating T lymphocytes in these three biopsies were quantified using a dPCR assay with the RNase P as an internal control and eight subgroups of TCRB probes and primers (subgroups A through H), essentially as described above in Example 5. The results are summarized in FIG. 6, which shows low variability in the TIL percentages and degrees of clonality that were detected according to the herein described methods in these three different biopsy samples, despite their being obtained from distinct sites in the tumor. These results demonstrate that there was low variation in TIL percentage (0.8%-2.3%) and low variation between biopsy samples as indicated by the degree of T cell receptor sequence, and hence T cell clonal, diversity (shown as the percent of each T cell class in A-H).

5

The accuracy of dPCR-based TIL quantification was performed using DNA from various dilutions of T cells, either in the presence or absence of 4000 MRC5 cells (a normal human lung cell line), to simulate a range of TIL detection down to roughly one T cell in a background of 1000 human cells. Digital PCR was performed using TCRB- and RNase P-specific primers essentially as described above in Examples 4 and 5. FIG. 7 shows that dPCR-based TIL quantification was accurate across a large dynamic range of T cell representation in a mixed cell population.

The various embodiments described above can be combined to provide further embodiments. All of the U.S. patents, U.S. patent application publications, U.S. patent applications, foreign patents, foreign patent applications and non-patent publications referred to in this specification and/or listed in the Application Data Sheet herein by reference, in their entirety. Aspects of the embodiments can be modified, if necessary to employ concepts of the various patents, applications and publications to provide yet further embodiments.

These and other changes can be made to the embodiments in light of the above-detailed description. In general, in the following claims, the terms used should not be construed to limit the claims to the specific embodiments disclosed in the specification and the claims, but should be construed to include all possible embodiments along with the full scope of equivalents to which such claims are entitled. Accordingly, the claims are not limited by the disclosure.

78
Example 9

Determining Accuracy of dPCR-Based Assay Across
a Large Sensitivity Range

10

The accuracy of dPCR-based TIL quantification was performed using DNA from various dilutions of T cells, either in the presence or absence of 4000 MRC5 cells (a normal human lung cell line), to simulate a range of TIL detection down to roughly one T cell in a background of 1000 human cells. Digital PCR was performed using TCRB- and RNase P-specific primers essentially as described above in Examples 4 and 5. FIG. 7 shows that dPCR-based TIL quantification was accurate across a large dynamic range of T cell representation in a mixed cell population.

The various embodiments described above can be combined to provide further embodiments. All of the U.S. patents, U.S. patent application publications, U.S. patent applications, foreign patents, foreign patent applications and non-patent publications referred to in this specification and/or listed in the Application Data Sheet herein by reference, in their entirety. Aspects of the embodiments can be modified, if necessary to employ concepts of the various patents, applications and publications to provide yet further embodiments.

These and other changes can be made to the embodiments in light of the above-detailed description. In general, in the following claims, the terms used should not be construed to limit the claims to the specific embodiments disclosed in the specification and the claims, but should be construed to include all possible embodiments along with the full scope of equivalents to which such claims are entitled. Accordingly, the claims are not limited by the disclosure.

SEQUENCE LISTING

```

<160> NUMBER OF SEQ ID NOS: 909

<210> SEQ ID NO 1
<211> LENGTH: 41
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
      Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV25-1_RN2v3
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (37)...(37)
<223> OTHER INFORMATION: Ribonucleotide base
<220> FEATURE:
<223> OTHER INFORMATION: 3' 3SpC3

<400> SEQUENCE: 1

ggagatcttt cctctgagtc aacagtctcc agaataagga c

```

41

```

<210> SEQ ID NO 2
<211> LENGTH: 35
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
      Synthetic primer

```

-continued

```

<220> FEATURE:
<223> OTHER INFORMATION: TRBV12-1_RN2v3
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (31)..(31)
<223> OTHER INFORMATION: Ribonucleotide base
<220> FEATURE:
<223> OTHER INFORMATION: 3' 3SpC3

<400> SEQUENCE: 2
ggattgattc tcagcacaga tgcctgatgt atcat                                35

<210> SEQ ID NO 3
<211> LENGTH: 37
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
    primer
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
    Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV12-5_RN2v3
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (33)..(33)
<223> OTHER INFORMATION: Ribonucleotide base
<220> FEATURE:
<223> OTHER INFORMATION: 3' 3SpC3

<400> SEQUENCE: 3
gattctcagc agagatgcct gatgcaactt tagccac                                37

<210> SEQ ID NO 4
<211> LENGTH: 46
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
    primer
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
    Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV2_RN2v3
<220> FEATURE:
<223> OTHER INFORMATION: 3' 3SpC3

<400> SEQUENCE: 4
aagtctgaaa tattcgatga tcaattctca gttgaaaggc cugatg                                46

<210> SEQ ID NO 5
<211> LENGTH: 31
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
    primer
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
    Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV16_RN2v3
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (27)..(27)
<223> OTHER INFORMATION: Ribonucleotide base
<220> FEATURE:
<223> OTHER INFORMATION: 3' 3SpC3

<400> SEQUENCE: 5

```

-continued

agctaaagtgc ctcccaaatt caccctgttag c

31

<210> SEQ ID NO 6
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV5-1_RN2v3
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (26)..(26)
<223> OTHER INFORMATION: Ribonucleotide base
<220> FEATURE:
<223> OTHER INFORMATION: 3' 3SpC3

<400> SEQUENCE: 6

cgattctcag ggccgcagg tt ctctaactct

30

<210> SEQ ID NO 7
<211> LENGTH: 34
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV14_RN2v3
<220> FEATURE:
<223> OTHER INFORMATION: 3' 3SpC3

<400> SEQUENCE: 7

tcttagctga aaggactgga gggacgtat u ctac

34

<210> SEQ ID NO 8
<211> LENGTH: 37
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV12-4_RN2v3
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (33)..(33)
<223> OTHER INFORMATION: Ribonucleotide base
<220> FEATURE:
<223> OTHER INFORMATION: 3' 3SpC3

<400> SEQUENCE: 8

gaggatcgat tctcagctaa gatgcctaat gcatcat

37

<210> SEQ ID NO 9
<211> LENGTH: 34
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:

-continued

```
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
      Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV28_RN2v3
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (30)..(30)
<223> OTHER INFORMATION: Ribonucleotide base
<220> FEATURE:
<223> OTHER INFORMATION: 3' 3SpC3
```

<400> SEQUENCE: 9

tccgtgggg tacagtgtct ctagagagaa gaag

34

```
<210> SEQ ID NO 10
<211> LENGTH: 39
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
      Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV27_RN2v3
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (35)..(35)
<223> OTHER INFORMATION: Ribonucleotide base
<220> FEATURE:
<223> OTHER INFORMATION: 3' 3SpC3
```

<400> SEQUENCE: 10

gatgttccctg aagggtacaa agtctctcga aaagagaag

39

```
<210> SEQ ID NO 11
<211> LENGTH: 35
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
      Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV5-4_RN2v3
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (31)..(31)
<223> OTHER INFORMATION: Ribonucleotide base
<220> FEATURE:
<223> OTHER INFORMATION: 3' 3SpC3
```

<400> SEQUENCE: 11

ctcctagatt ctcagggtctc cagttcccta attat

35

```
<210> SEQ ID NO 12
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
      Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV7-1_RN2v3
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (26)..(26)
```

-continued

<223> OTHER INFORMATION: Ribonucleotide base
<220> FEATURE:
<223> OTHER INFORMATION: 3' 3SpC3
<400> SEQUENCE: 12

cgtgatcggt tctctgcaca gaggtctgag 30

<210> SEQ ID NO 13
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV19_RN2v3
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (26)..(26)
<223> OTHER INFORMATION: Ribonucleotide base
<220> FEATURE:
<223> OTHER INFORMATION: 3' 3SpC3

<400> SEQUENCE: 13
gctgaagggt acagcgtctc tcgggagaag 30

<210> SEQ ID NO 14
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV5-3_RN2v3
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (26)..(26)
<223> OTHER INFORMATION: Ribonucleotide base
<220> FEATURE:
<223> OTHER INFORMATION: 3' 3SpC3

<400> SEQUENCE: 14
cgattctcag ggcgccagtt ccatgactgt 30

<210> SEQ ID NO 15
<211> LENGTH: 38
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV9_RN2v3
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (34)..(34)
<223> OTHER INFORMATION: Ribonucleotide base
<220> FEATURE:
<223> OTHER INFORMATION: 3' 3SpC3

<400> SEQUENCE: 15
caacagttcc ctgacttgca ctctgaacta aacctgag 38

-continued

```

<210> SEQ ID NO 16
<211> LENGTH: 38
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
      Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV6-7_RN2v3
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (34)..(34)
<223> OTHER INFORMATION: Ribonucleotide base
<220> FEATURE:
<223> OTHER INFORMATION: 3' 3SpC3

<400> SEQUENCE: 16

agaagttccc aatggctaca atgtctccag atcaaaca

```

38

```

<210> SEQ ID NO 17
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
      Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV6-4_RN2v3
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (32)..(32)
<223> OTHER INFORMATION: Ribonucleotide base
<220> FEATURE:
<223> OTHER INFORMATION: 3' 3SpC3

<400> SEQUENCE: 17

```

```
aagtccctga tggttatagt gtctccagag caaaaca
```

36

```

<210> SEQ ID NO 18
<211> LENGTH: 34
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
      Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV6-1_RN2v3
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (30)..(30)
<223> OTHER INFORMATION: Ribonucleotide base
<220> FEATURE:
<223> OTHER INFORMATION: 3' 3SpC3

<400> SEQUENCE: 18

```

```
gtcccccaatg gctacaatgt ctccagatta aaca
```

34

```

<210> SEQ ID NO 19
<211> LENGTH: 32
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

```

-continued

```

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
      Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV7-9_RN2v3
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (28)..(28)
<223> OTHER INFORMATION: Ribonucleotide base
<220> FEATURE:
<223> OTHER INFORMATION: 3' 3SpC3

```

<400> SEQUENCE: 19

ttctctgcag agaggcctaa gggatcttc tc

32

```

<210> SEQ_ID NO 20
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
      Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV7-9_RN2v3
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (25)..(25)
<223> OTHER INFORMATION: Ribonucleotide base
<220> FEATURE:
<223> OTHER INFORMATION: 3' 3SpC3

```

<400> SEQUENCE: 20

gcccaacgat cgggttttg cagtcaggc

29

```

<210> SEQ_ID NO 21
<211> LENGTH: 28
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
      Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV7-4_RN2v3
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (24)..(24)
<223> OTHER INFORMATION: Ribonucleotide base
<220> FEATURE:
<223> OTHER INFORMATION: 3' 3SpC3

```

<400> SEQUENCE: 21

ccagtggtcg gttctctgca gagaggcc

28

```

<210> SEQ_ID NO 22
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
      Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV5-6_RN2v3

```

-continued

<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (29)..(29)
<223> OTHER INFORMATION: Ribonucleotide base
<220> FEATURE:
<223> OTHER INFORMATION: 3' 3SpC3

<400> SEQUENCE: 22

gcaacttccc tgatcgattc tcaggtcacc agt

33

<210> SEQ ID NO 23
<211> LENGTH: 38
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV5-6_RN2v3
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (34)..(34)
<223> OTHER INFORMATION: Ribonucleotide base
<220> FEATURE:
<223> OTHER INFORMATION: 3' 3SpC3

<400> SEQUENCE: 23

cagaggaaac ttccctccta gatttcagg tcgccagt

38

<210> SEQ ID NO 24
<211> LENGTH: 31
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV7-8_RN2v3
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (27)..(27)
<223> OTHER INFORMATION: Ribonucleotide base
<220> FEATURE:
<223> OTHER INFORMATION: 3' 3SpC3

<400> SEQUENCE: 24

gcccagtat cgcttctttg cagaaaggcc t

31

<210> SEQ ID NO 25
<211> LENGTH: 31
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV12-2_RN2v3
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (27)..(27)
<223> OTHER INFORMATION: Ribonucleotide base
<220> FEATURE:
<223> OTHER INFORMATION: 3' 3SpC3

-continued

<400> SEQUENCE: 25

cgattcttag ctgagaggcc tggatggatca t

31

<210> SEQ ID NO 26
<211> LENGTH: 35
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV15_RN2v3
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (31)..(31)
<223> OTHER INFORMATION: Ribonucleotide base
<220> FEATURE:
<223> OTHER INFORMATION: 3' 3SpC3

<400> SEQUENCE: 26

aggccgaaca cttctttctg ctttcttgac atccg

35

<210> SEQ ID NO 27
<211> LENGTH: 32
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV6-2_RN2v3
<220> FEATURE:
<223> OTHER INFORMATION: 3' 3SpC3

<400> SEQUENCE: 27

caaaggagag gtccctgtat gctacaaugt ct

32

<210> SEQ ID NO 28
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV23-1_RN2v3
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (29)..(29)
<223> OTHER INFORMATION: Ribonucleotide base
<220> FEATURE:
<223> OTHER INFORMATION: 3' 3SpC3

<400> SEQUENCE: 28

gattctcatc tcaatgcccc aagaacgcac cct

33

<210> SEQ ID NO 29
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic

-continued

```

primer
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
    Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV10-2_RN2v3
<220> FEATURE:
<223> OTHER INFORMATION: 3' 3SpC3

<400> SEQUENCE: 29

```

cagataaaagg agaagtcccc gatggctatg tugtct

36

```

<210> SEQ ID NO 30
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
    primer
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
    Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV30_RN2v3
<220> FEATURE:
<223> OTHER INFORMATION: 3' 3SpC3

<400> SEQUENCE: 30

```

caggaccggc agttcatctt gagtuctaa

29

```

<210> SEQ ID NO 31
<211> LENGTH: 41
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
    primer
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
    Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV10-3_RN2v3
<220> FEATURE:
<223> OTHER INFORMATION: 3' 3SpC3

<400> SEQUENCE: 31

```

agataactgac aaaggagaag tcttcagatgg ctatagugtc t

41

```

<210> SEQ ID NO 32
<211> LENGTH: 35
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
    primer
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
    Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV6-6_RN2v3
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (31)..(31)
<223> OTHER INFORMATION: Ribonucleotide base
<220> FEATURE:
<223> OTHER INFORMATION: 3' 3SpC3

<400> SEQUENCE: 32

```

gacaaaggag aagtcccgaa tggctacaac gtctc

35

<210> SEQ ID NO 33

-continued

```

<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
      Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV13_RN2v3
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (32)..(32)
<223> OTHER INFORMATION: Ribonucleotide base
<220> FEATURE:
<223> OTHER INFORMATION: 3' 3SpC3

<400> SEQUENCE: 33

ccctgatcga ttctcagctc aacagtttag tgacta

```

36

```

<210> SEQ ID NO 34
<211> LENGTH: 35
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
      Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV4-1_RN2v3
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (31)..(31)
<223> OTHER INFORMATION: Ribonucleotide base
<220> FEATURE:
<223> OTHER INFORMATION: 3' 3SpC3

<400> SEQUENCE: 34

cctgaatgcc ccaacagctc tctcttaaac cttca

```

35

```

<210> SEQ ID NO 35
<211> LENGTH: 35
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
      Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV4-3_RN2v3
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (31)..(31)
<223> OTHER INFORMATION: Ribonucleotide base
<220> FEATURE:
<223> OTHER INFORMATION: 3' 3SpC3

<400> SEQUENCE: 35

cctgaatgcc ccaacagctc tcacttatttc cttca

```

35

```

<210> SEQ ID NO 36
<211> LENGTH: 42
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:

```

-continued

<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV26_RN2v3
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (38)..(38)
<223> OTHER INFORMATION: Ribonucleotide base
<220> FEATURE:
<223> OTHER INFORMATION: 3' 3SpC3

<400> SEQUENCE: 36

ggagatgtct ctgagaggta tcatgtttct taaaatacta ta

42

<210> SEQ ID NO 37
<211> LENGTH: 42
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
primer
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV6-8_RN2v3
<220> FEATURE:
<223> OTHER INFORMATION: 3' 3SpC3

<400> SEQUENCE: 37

tacaatgtct ctagattaaa cacagaggat ttcccacuca gg

42

<210> SEQ ID NO 38
<211> LENGTH: 35
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
primer
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV3-2_RN2v3
<220> FEATURE:
<223> OTHER INFORMATION: 3' 3SpC3

<400> SEQUENCE: 38

ttctcacctg actctccaga caaaagctcat utaaa

35

<210> SEQ ID NO 39
<211> LENGTH: 35
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
primer
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV11-2_RN2v3
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (31)..(31)
<223> OTHER INFORMATION: Ribonucleotide base
<220> FEATURE:
<223> OTHER INFORMATION: 3' 3SpC3

<400> SEQUENCE: 39

cctaaggatc gattttctgc agagaggctc aaagg

35

-continued

```

<210> SEQ ID NO 40
<211> LENGTH: 34
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
      Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV2_RN2v3
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (30)..(30)
<223> OTHER INFORMATION: Ribonucleotide base
<220> FEATURE:
<223> OTHER INFORMATION: 3' 3SpC3

<400> SEQUENCE: 40

cctgaatgcc ctgacagctc tcgcattatac ctcc

```

34

```

<210> SEQ ID NO 41
<211> LENGTH: 42
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
      Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV3-1_RN2v3
<220> FEATURE:
<223> OTHER INFORMATION: 3' 3SpC3

<400> SEQUENCE: 41

gcttctcacc taaatctcca gacaaagctc actttaauct tc

```

42

```

<210> SEQ ID NO 42
<211> LENGTH: 34
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
      Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV29-1_RN2v3
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (30)..(30)
<223> OTHER INFORMATION: Ribonucleotide base
<220> FEATURE:
<223> OTHER INFORMATION: 3' 3SpC3

<400> SEQUENCE: 42

```

```

catcagccgc ccaaacctaa catttcac ac tctg

```

34

```

<210> SEQ ID NO 43
<211> LENGTH: 34
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
      Synthetic primer

```

-continued

<220> FEATURE:
<223> OTHER INFORMATION: TRBV18_RN2v3
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (30)..(30)
<223> OTHER INFORMATION: Ribonucleotide base
<220> FEATURE:
<223> OTHER INFORMATION: 3' 3SpC3

<400> SEQUENCE: 43

attttctgct gaatttccca aagaggggccc cagc

34

<210> SEQ ID NO 44
<211> LENGTH: 34
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV17_RN2v3
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (30)..(30)
<223> OTHER INFORMATION: Ribonucleotide base
<220> FEATURE:
<223> OTHER INFORMATION: 3' 3SpC3

<400> SEQUENCE: 44

attcacagct gaaagaccta acggaacgtc ttcc

34

<210> SEQ ID NO 45
<211> LENGTH: 31
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV20-1_RN2v3
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (27)..(27)
<223> OTHER INFORMATION: Ribonucleotide base
<220> FEATURE:
<223> OTHER INFORMATION: 3' 3SpC3

<400> SEQUENCE: 45

caagcctgac cttgtccact ctgacagtga c

31

<210> SEQ ID NO 46
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV7-6_RN2v3
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (25)..(25)
<223> OTHER INFORMATION: Ribonucleotide base
<220> FEATURE:

-continued

<223> OTHER INFORMATION: 3' 3SpC3

<400> SEQUENCE: 46

ggttctctgc agagaggcct gagggatcc

29

<210> SEQ ID NO 47

<211> LENGTH: 39

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<220> FEATURE:

<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic primer

<220> FEATURE:

<223> OTHER INFORMATION: TRBV24-1_RN2v3

<220> FEATURE:

<221> NAME/KEY: modified_base

<222> LOCATION: (35)..(35)

<223> OTHER INFORMATION: Ribonucleotide base

<220> FEATURE:

<223> OTHER INFORMATION: 3' 3SpC3

<400> SEQUENCE: 47

gagagatctc tgatggatac agtgtctctc gacaggcac

39

<210> SEQ ID NO 48

<211> LENGTH: 31

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<220> FEATURE:

<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic primer

<220> FEATURE:

<223> OTHER INFORMATION: TRBV7-2_RN2v3

<220> FEATURE:

<221> NAME/KEY: modified_base

<222> LOCATION: (27)..(27)

<223> OTHER INFORMATION: Ribonucleotide base

<220> FEATURE:

<223> OTHER INFORMATION: 3' 3SpC3

<400> SEQUENCE: 48

gatcgcttct ctgcagagag gactggggga t

31

<210> SEQ ID NO 49

<211> LENGTH: 34

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<220> FEATURE:

<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic primer

<220> FEATURE:

<223> OTHER INFORMATION: TRBV6-9_RN2v3

<220> FEATURE:

<223> OTHER INFORMATION: 3' 3SpC3

<400> SEQUENCE: 49

aaggagaagt ccccgatggc tacaatgtau ccag

34

<210> SEQ ID NO 50

<211> LENGTH: 34

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

-continued

<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV6-5_RN2v3
<220> FEATURE:
<223> OTHER INFORMATION: 3' 3SpC3

<400> SEQUENCE: 50

aaggagaagt ccccaatggc tacaatgtcu ccag

34

<210> SEQ ID NO 51
<211> LENGTH: 35
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV5-5_RN2v3
<220> FEATURE:
<223> OTHER INFORMATION: 3' 3SpC3

<400> SEQUENCE: 51

aagagggaaac ttccctgatc gattctcagc ucgcc

35

<210> SEQ ID NO 52
<211> LENGTH: 40
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV10-1_RN2v3
<220> FEATURE:
<223> OTHER INFORMATION: 3' 3SpC3

<400> SEQUENCE: 52

gacactaaca aaggagaagt ctcagatggc tacagugtct

40

<210> SEQ ID NO 53
<211> LENGTH: 40
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBJ1-1_RN2v3
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (36)..(36)
<223> OTHER INFORMATION: Ribonucleotide base
<220> FEATURE:
<223> OTHER INFORMATION: 3' 3SpC3

<400> SEQUENCE: 53

ttacctacaa ctgtgagtc ggtgccttgt ccaaagaaaag

40

-continued

```

<210> SEQ ID NO 54
<211> LENGTH: 35
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
      Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBJ1-2_RN2v3
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (31)..(31)
<223> OTHER INFORMATION: Ribonucleotide base
<220> FEATURE:
<223> OTHER INFORMATION: 3' 3SpC3

<400> SEQUENCE: 54

tacaacggtt aacctgggcc ccgaaccgaa ggtgt

```

35

```

<210> SEQ ID NO 55
<211> LENGTH: 39
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
      Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBJ1-3_RN2v3
<220> FEATURE:
<223> OTHER INFORMATION: 3' 3SpC3

<400> SEQUENCE: 55

```

```
acctacaaca gtgagccaaac ttccctctcc aaaaatata
```

39

```

<210> SEQ ID NO 56
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
      Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBJ1-4_RN2v3
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (32)..(32)
<223> OTHER INFORMATION: Ribonucleotide base
<220> FEATURE:
<223> OTHER INFORMATION: 3' 3SpC3

<400> SEQUENCE: 56

```

```
caagacagag agctgggttc cactgccaaa aaacag
```

36

```

<210> SEQ ID NO 57
<211> LENGTH: 38
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
      Synthetic primer

```

-continued

```

<220> FEATURE:
<223> OTHER INFORMATION: TRBJ1-5_RN2v3
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (34)..(34)
<223> OTHER INFORMATION: Ribonucleotide base
<220> FEATURE:
<223> OTHER INFORMATION: 3' 3SpC3

<400> SEQUENCE: 57

```

accttagatg gagagtcgag tcccatcacc aaaatgct 38

```

<210> SEQ ID NO 58
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
      Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBJ1-6_RN2v3
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (29)..(29)
<223> OTHER INFORMATION: Ribonucleotide base
<220> FEATURE:
<223> OTHER INFORMATION: 3' 3SpC3

<400> SEQUENCE: 58

```

tcacagttag cctggtcccc ttcccaaagt gga 33

```

<210> SEQ ID NO 59
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
      Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBJ2-1_RN2v3
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (26)..(26)
<223> OTHER INFORMATION: Ribonucleotide base
<220> FEATURE:
<223> OTHER INFORMATION: 3' 3SpC3

<400> SEQUENCE: 59

```

cggtgagccg tgtccctggc ccgaagaact 30

```

<210> SEQ ID NO 60
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
      Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBJ2_2RN2v3
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (32)..(32)
<223> OTHER INFORMATION: Ribonucleotide base
<220> FEATURE:

```

-continued

<223> OTHER INFORMATION: 3' 3SpC3

<400> SEQUENCE: 60

ccagtagcggt cagcctagag ccttctccaa aaaaca

36

<210> SEQ ID NO 61

<211> LENGTH: 31

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<220> FEATURE:

<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic primer

<220> FEATURE:

<223> OTHER INFORMATION: TRBJ2-3_RN2v3

<220> FEATURE:

<221> NAME/KEY: modified_base

<222> LOCATION: (27)..(27)

<223> OTHER INFORMATION: Ribonucleotide base

<220> FEATURE:

<223> OTHER INFORMATION: 3' 3SpC3

<400> SEQUENCE: 61

actgtcagcc gggtgcctgg gccaaaatac t

31

<210> SEQ ID NO 62

<211> LENGTH: 27

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<220> FEATURE:

<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic primer

<220> FEATURE:

<223> OTHER INFORMATION: TRBJ2-3_RN2v3

<220> FEATURE:

<221> NAME/KEY: modified_base

<222> LOCATION: (23)..(23)

<223> OTHER INFORMATION: Ribonucleotide base

<220> FEATURE:

<223> OTHER INFORMATION: 3' 3SpC3

<400> SEQUENCE: 62

agagccgggt cccggcgccg aagtact

27

<210> SEQ ID NO 63

<211> LENGTH: 27

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<220> FEATURE:

<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic primer

<220> FEATURE:

<223> OTHER INFORMATION: TRBJ2-5_RN2v3

<220> FEATURE:

<221> NAME/KEY: modified_base

<222> LOCATION: (23)..(23)

<223> OTHER INFORMATION: Ribonucleotide base

<220> FEATURE:

<223> OTHER INFORMATION: 3' 3SpC3

<400> SEQUENCE: 63

ggagccgcgt gcctggcccg aagtact

27

-continued

```

<210> SEQ ID NO 64
<211> LENGTH: 28
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
      Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBJ2-6_RN2v3
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (24)..(24)
<223> OTHER INFORMATION: Ribonucleotide base
<220> FEATURE:
<223> OTHER INFORMATION: 3' 3SpC3

<400> SEQUENCE: 64

```

gtcagcctgc tgccggcccc gaaagtca

28

```

<210> SEQ ID NO 65
<211> LENGTH: 28
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
      Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBJ2-7_RN2v3
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (24)..(24)
<223> OTHER INFORMATION: Ribonucleotide base
<220> FEATURE:
<223> OTHER INFORMATION: 3' 3SpC3

<400> SEQUENCE: 65

```

gtgagcctgg tgcccgcccc gaagtact

28

```

<210> SEQ ID NO 66
<211> LENGTH: 26
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      probe
<220> FEATURE:
<223> OTHER INFORMATION: TCRB V7 family-specific real time PCR probe
<220> FEATURE:
<223> OTHER INFORMATION: 3' TET(tetrachlorofluorescein) or 3BHQ_1(4-(2-
      nitro-4-toloyl)diazo)-2'-methoxy-5'-methyl-azobenzene-4"- (N-ethyl)-
      N-ethyl-2-cyanoethyl-(N,N-diisopropyl)-phosphoramidite)

<400> SEQUENCE: 66

```

gggactcagc ygtgtatctc tgtgcc

26

```

<210> SEQ ID NO 67
<211> LENGTH: 284
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV1*01

<400> SEQUENCE: 67

```

-continued

gatactggaa ttacccagac accaaaatac ctggtcacag caatggggag taaaaggaca	60
atgaaacgtg agcatctggg acatgattct atgtattggt acagacagaa agctaagaaa	120
tccctggagt tcatgtttta ctacaactgt aaggaattca ttgaaaacaa gactgtgcc	180
aatcacttca cacctgaatg ccctgacagc tctcgcttat accttcatgt ggtcgactg	240
cagcaagaag actcagctgc gtatctctgc accagcagcc aaga	284
<210> SEQ ID NO 68	
<211> LENGTH: 289	
<212> TYPE: DNA	
<213> ORGANISM: Artificial Sequence	
<220> FEATURE:	
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide	
<220> FEATURE:	
<223> OTHER INFORMATION: TRBV2*01	
<400> SEQUENCE: 68	
gaacctgaag tcacccagac tcccagccat caggtcacac agatgggaca ggaagtgtac	60
ttgcgtgtg tccccatctc taatcaactt tacttctatt ggtacagaca aatcttggc	120
agaaaagtca gtttctggtt tcctttata ataatgaaat ctcagagaag tctgaaatat	180
tcatgtatca attctcagtt gaaaggcctg atggatcaa tttcaactctg aagatccgg	240
ccacaaaagct ggaggactca gccatgtact tctgtgccag cagtgaagc	289
<210> SEQ ID NO 69	
<211> LENGTH: 288	
<212> TYPE: DNA	
<213> ORGANISM: Artificial Sequence	
<220> FEATURE:	
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide	
<220> FEATURE:	
<223> OTHER INFORMATION: TRBV2*03	
<400> SEQUENCE: 69	
gaacctgaag tcacccagac tcccagccat caggtcacac agatgggaca ggaagtgtac	60
ttgcgtgtg tccccatctc taatcaactt tacttctatt ggtacagaca aatcttggg	120
cagaaaagtca agtttctgggt tccttttat aataatgaaa tctcagagaa gtctgaaata	180
ttcgatgtac aattctcagt tgagaggcct gatggatcaa atttcactct gaagatccgg	240
tccacaaaagc tggaggactc agccatgtac ttctgtgccca gcagtgaac	288
<210> SEQ ID NO 70	
<211> LENGTH: 287	
<212> TYPE: DNA	
<213> ORGANISM: Artificial Sequence	
<220> FEATURE:	
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide	
<220> FEATURE:	
<223> OTHER INFORMATION: TRBV3-1*01	
<400> SEQUENCE: 70	
gacacagctg tttccagac tccaaaatac ctggtcacac agatggaaaa cgacaagtcc	60
attnaatgtg aacaaaatct gggccatgt actatgtatt ggtataaaca ggactctaag	120
aaatttctga agataatgtt tagtacaat aataaggagc tcattataaa tgaaacagtt	180
ccaaatcgct tctcacctaa atctccagac aaagctcaat taaatcttca catcaattcc	240
ctggagcttg gtgactctgc tgtgtatttc tgtgccagca gccaaga	287

-continued

<210> SEQ ID NO 71
<211> LENGTH: 279
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV3-1*02

<400> SEQUENCE: 71

gacacagctg tttccagac tccaaaatac ctggcacac agatggaaa cgacaagtcc	60
attnaatgtg aacaaaatct gggccatgtt actatgtatt ggtataaaca ggactctaag	120
aaatttctga agataatgtt tagctacaat aacaaggaga tcattataaa tgaaacagtt	180
ccaaatcgat tctcacctaa atctccagac aaagcttaat taaatctca catcaattcc	240
ctggagcttg gtgactctgc tgtgtatttc tgtgccagc	279

<210> SEQ ID NO 72
<211> LENGTH: 287
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV3-2*01

<400> SEQUENCE: 72

gacacagccg tttccagac tccaaaatac ctggcacac agatggaaa aaaggagtct	60
cttaatgag aacaaaatct gggccataat gctatgtatt ggtataaaca ggactctaag	120
aaatttctga agacaatgtt tatctacagt aacaaggagc caattttaaa tgaaacagtt	180
ccaaatcgct tctcacctga ctctccagac aaagcttatt taaatctca catcaattcc	240
ctggagcttg gtgactctgc tgtgtatttc tgtgccagc gccaaga	287

<210> SEQ ID NO 73
<211> LENGTH: 287
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV3-2*02

<400> SEQUENCE: 73

gacacagccg tttccagac tccaaaatac ctggcacac agatggaaa aaaggagtct	60
cttaatgag aacaaaatct gggccataat gctatgtatt ggtataaaca ggactctaag	120
aaatttctga agacaatgtt tatctacagt aacaaggagc caattttaaa tgaaacagtt	180
ccaaatcgct tctcacctga ctctccagac aaagttatt taaatctca catcaattcc	240
ctggagcttg gtgactctgc tgtgtatttc tgtgccagc gccaaga	287

<210> SEQ ID NO 74
<211> LENGTH: 285
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV3-2*03

-continued

<400> SEQUENCE: 74

```
gacacagccg tttcccagac tcacaaatac ctggtcacac agacgggaaa aaaggagtct      60
cttaaatgag aacaaaatct gggccataat gctatgtatt ggtataaaca ggactctaag     120
aaatttctga agacaatgtt tatctacagt aacaaggagc caatttaaa tgaaacagtt     180
ccaaatcgct tctcacctga ctctccagac aaagttcatt taaatcttca catcaattcc     240
ctggagcttg gtgactctgc tgtgtatttc tgtgccagca gccaa                         285
```

<210> SEQ ID NO 75
<211> LENGTH: 287
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV4-1*01

<400> SEQUENCE: 75

```
gacactgaag ttacccagac accaaaacac ctggtcatgg gaatgacaaa taagaagtct      60
ttgaaatgtg aacaacatat ggggcacagg gctatgtatt ggtacaagca gaaagctaa     120
aagccaccgg agctcatgtt tgtctacagc tatgagaaac tctctataaa tgaaagtgtg     180
ccaagtcgct tctcacctga atgccccaaac agctctcttca cctacacgccc             240
ctgcagccag aagactcagc cctgtatctc tgccgcagca gccaaaga                         287
```

<210> SEQ ID NO 76
<211> LENGTH: 258
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV4-1*02

<400> SEQUENCE: 76

```
cacctggta tggaaatgac aaataagaag tctttgaaat gtgaacaaca tatggggcac      60
agggcaatgt attggtaaaaa gcagaaagct aagaagccac cggagatcat gtttgtctac     120
agctatgaga aactcttat aatgaaagt gtgccaagtc gtttctcacc tgaatgcccc     180
aacagctctc tcttaaacct tcacctacac gcccgtcagc cagaagactc agccctgtat     240
ctctgcgcca gcagccaa                                         258
```

<210> SEQ ID NO 77
<211> LENGTH: 287
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV4-2*01

<400> SEQUENCE: 77

```
gaaacgggag ttacgcagac accaagacac ctggtcatgg gaatgacaaa taagaagtct      60
ttgaaatgtg aacaacatct gggccataac gctatgtatt ggtacaagca aagtgtctaa     120
aagccactgg agctcatgtt tgtctacaac tttaaagaac agactgaaaa caacagtggtg     180
ccaagtcgct tctcacctga atgccccaaac agctctcaact tattccttca cctacacacc     240
```

-continued

ctgcagccag aagactcgac cctgtatctc tgtgccagca gccaaga 287

<210> SEQ ID NO 78
<211> LENGTH: 282
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV4-2*02

<400> SEQUENCE: 78

gaaacgggag ttacgcagac accaagacac ctggcatgg gaatgacaaa taagaagtct 60
ttgaaatgtg aacaacatct gggcataac gctatgtatt ggtacaagca aagtgctaag 120
aagccactgg agctcatgtt tgtctacaac tttaaagaac agactgaaaa caacagtgtg 180
ccaagtcgct tctcacctga atgccccaac agctctcaact tatgccttca cctacacacc 240
ctgcagccag aagactcgac cctgtatctc tgtgccagca cc 282

<210> SEQ ID NO 79
<211> LENGTH: 287
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV4-3*01

<400> SEQUENCE: 79

gaaacgggag ttacgcagac accaagacac ctggcatgg gaatgacaaa taagaagtct 60
ttgaaatgtg aacaacatct gggcataac gctatgtatt ggtacaagca aagtgctaag 120
aagccactgg agctcatgtt tgtctacagt cttgaagaac gggtgaaaa caacagtgtg 180
ccaagtcgct tctcacctga atgccccaac agctctcaact tatgccttca cctacacacc 240
ctgcagccag aagactcgac cctgtatctc tgccagca gccaaga 287

<210> SEQ ID NO 80
<211> LENGTH: 282
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV4-3*02

<400> SEQUENCE: 80

gaaacgggag ttacgcagac accaagacac ctggcatgg gaatgacaaa taagaagtct 60
ttgaaatgtg aacaacatct gggcataac gctatgtatt ggtacaagca aagtgctaag 120
aagccactgg agctcatgtt tgtctacagt cttgaagaac gggtgaaaa caacagtgtg 180
ccaagtcgct tctcacctga atgccccaac agctctcaact tatgccttca cctacacacc 240
ctgcagccag aagactcgac cctgtatctc tgccagca gc 282

<210> SEQ ID NO 81
<211> LENGTH: 282
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic

-continued

polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV4-3*3

<400> SEQUENCE: 81

```

gaaacgggag ttacgcagac accaagacac ctggtcatgg gaatgacaaa taagaagtct      60
ttgaaatgtg aacaacatct gggcataac gctatgtatt ggtacaagca aagtgctaag      120
aagccactgg agctcatgtt tgtctacagt cttgaagaac gtgtgaaaa caacagtgtg      180
ccaagtcgct tctcacctga atgccccaac agctctcact tattccttca cctacacacc      240
ctgcagccag aagactcgcc cctgtatctc tgccgcagca gc                           282

```

<210> SEQ ID NO 82
<211> LENGTH: 231
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV4-3*04

<400> SEQUENCE: 82

```

aagaagtctt tgaaatgtga acaacatctg gggcataacg ctatgtattg gtacaagcaa      60
agtgctaaga agccactgga gctcatgttt gtctacagtct ttgaagaacg gggtgaaaac      120
aacagtgtgc caagtcgctt ctcacctgaa tgccccaaaca gctctcactt attccttac      180
ctacacaccc tgcagccaga agactcgcc ctgtatctc ggcgcagcag c                           231

```

<210> SEQ ID NO 83
<211> LENGTH: 286
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV5-1*01

<400> SEQUENCE: 83

```

aaggctggag tcactcaaac tccaagatat ctgatcaaaa cgagaggaca gcaagtgaca      60
ctgagctgtct cccstatctc tgggcatagg agtgtatcct ggtaccaaca gaccccgaga      120
cagggccttc agttccttta tgaataacttc agtgagacac agagaaacaa aggaaaacttc      180
cctgggtcgat tctcaggcg ccagttctct aactctcgct ctgagatgaa tgtgagcacc      240
ttggagctgg gggactcgcc ccttatctt tgccgcagca gcttgg                           286

```

<210> SEQ ID NO 84
<211> LENGTH: 285
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV5-1*02

<400> SEQUENCE: 84

```

agggctgggg tcactcaaac tccaagacat ctgatcaaaa cgagaggaca gcaagtgaca      60
ctgggctgtct cccstatctc tgggcatagg agtgtatcct ggtaccaaca gacccttagga      120
cagggccttc agttccttta tgaataacttc agtgagacac agagaaacaa aggaaaacttc      180

```

-continued

cttggtcgat tctcagggcg ccagttctct aactctcgct ctgagatgaa tgtgagcacc	240
ttggagctgg gggactcgcc ccttatctt tgccgcagcg ctgc	285

<210> SEQ ID NO 85
<211> LENGTH: 286
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV5-3*01

<400> SEQUENCE: 85

gaggctggag tcacccaaag tcccacacac ctgatcaaaa cgagaggaca gcaagtgact	60
ctgagatgct ctcstatctc tggcacagc agtgtgtcct ggtaccaaca ggccccgggt	120
cagggggccc agtttatctt tgaatatgct aatgagttaa ggagatcaga aggaaacttc	180
cctaatcgat tctcagggcg ccagttccat gactattgct ctgagatgaa tgtgagtgcc	240
ttggagctgg gggactcgcc cctgtatctc tgtgccagaa gcttgg	286

<210> SEQ ID NO 86
<211> LENGTH: 286
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV5-3*02

<400> SEQUENCE: 86

gaggctggag tcacccaaag tcccacacac ctgatcaaaa cgagaggaca gcaagtgact	60
ctgagatgct ctcstatctc tggcacagc agtgtgtcct ggtaccaaca ggccccgggt	120
cagggggccc agtttatctt tgaatatgct aatgagttaa ggagatcaga aggaaacttc	180
cctaatcgat tctcagggcg ccagttccat gactattgct ctgagatgaa tgtgagtgcc	240
ttggagctgg gggactcgcc cctgtatctc tgtgccagaa gcttgg	286

<210> SEQ ID NO 87
<211> LENGTH: 286
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV5-4*01

<400> SEQUENCE: 87

gagactggag tcacccaaag tcccacacac ctgatcaaaa cgagaggaca gcaagtgact	60
ctgagatgct cttctcagtc tggcacaca actgtgtcct ggtaccaaca ggccctgggt	120
cagggggccc agtttatctt tcagtattat agggaggaag agaatggcag aggaaacttc	180
cctcctagat tctcaggtct ccagttccct aattatgct ctgagctgaa tgtgaacgcc	240
ttggagctgg acgactcgcc cctgtatctc tgtgccagca gcttgg	286

<210> SEQ ID NO 88
<211> LENGTH: 282
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

-continued

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:

<223> OTHER INFORMATION: TRBV5-4*02

<400> SEQUENCE: 88

gagactggag tcacccaaag tcccacacac ctgatcaaaa cgagaggaca gcaagtgact	60
ctgagatgt cttctcagtc tgggcacaac actgtgtcct ggtaccaaca ggccctgggt	120
cagggggccc agtttatctt tcagtattat agggaggaag agaatggcag aggaaacttc	180
cctcttagat tctcaggctc ccagttccct aattataact ctgagctgaa tgtgaacgcc	240
ttggagctgg acgactcgcc cctgtatctc tgtgccagca gc	282

<210> SEQ ID NO 89

<211> LENGTH: 234

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:

<223> OTHER INFORMATION: TRBV5-4*03

<400> SEQUENCE: 89

cagcaagtga cactgagatg ctcttctcag tctggcaca acactgtgtc ctggcacaa	60
caggccctgg gtcaggggcc ccagtttac ttctcaggatt atagggagga agagaatggc	120
agagaaaact tccctcttag attctcaggc ctccagttc ctaattatag ctctgagctg	180
aatgtgaacg cttggagct ggacgactcg gccctgtatc tctgtgccag cagc	234

<210> SEQ ID NO 90

<211> LENGTH: 192

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:

<223> OTHER INFORMATION: TRBV5-4*04

<400> SEQUENCE: 90

actgtgtcct ggtaccaaca ggccctgggt cagggggccc agtttatctt tcagtattat	60
agggaggaag agaatggcag aggaaactcc ctccttagat tctcaggctc ccagttccct	120
aattatagct ctgagctgaa tgtgaacgcc ttggagctgg acgactcgcc cctgtatctc	180
tgtgccagca gc	192

<210> SEQ ID NO 91

<211> LENGTH: 286

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:

<223> OTHER INFORMATION: TRBV5-5*01

<400> SEQUENCE: 91

gacgctggag tcacccaaag tcccacacac ctgatcaaaa cgagaggaca gcaagtgact	60
ctgagatgt ctcctatctc tgggcacaag agtgtgtcct ggtaccaaca ggccctgggt	120
cagggggccc agtttatctt tcagtattat gagaaagaag agagaggaag aggaaacttc	180
cctgatcgat tctcaggctc ccagttccct aactatagct ctgagctgaa tgtgaacgcc	240

-continued

ttgttgctgg gggactcggc cctgttatctc tgtgccagca gcttgg 286

<210> SEQ ID NO 92
<211> LENGTH: 282
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV5-5*02

<400> SEQUENCE: 92

gacgctggag tcacccaaag tcccacacac ctgatcaaaa cgagaggaca gcacgtgact 60
ctgagatgct ctcstatctc tgggcacaag agtgtgtcct ggtaccaaca ggtcctgggt 120
cagggggcccc agtttatctt tcagtattat gagaaagaag agagaggaag aggaaacttc 180
cctgatcgat tctcagctcg ccagttccct aactatacgct ctgagctgaa tgtgaacgcc 240
ttgttgctgg gggactcggc cctgttatctc tgtgccagca gc 282

<210> SEQ ID NO 93
<211> LENGTH: 282
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV5-5*03

<400> SEQUENCE: 93

gacgctggag tcacccaaag tcccacacac ctgatcaaaa cgagaggaca gcaagtgact 60
ctgagatgct ctcstatctc tgagcacaag agtgtgtcct ggtaccaaca ggtcctgggt 120
cagggggcccc agtttatctt tcagtattat gagaaagaag agagaggaag aggaaacttc 180
cctgatcgat tctcagctcg ccagttccct aactatacgct ctgagctgaa tgtgaacgcc 240
ttgttgctgg gggactcggc cctgttatctc tgtgccagca gc 282

<210> SEQ ID NO 94
<211> LENGTH: 286
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV5-6*01

<400> SEQUENCE: 94

gacgctggag tcacccaaag tcccacacac ctgatcaaaa cgagaggaca gcaagtgact 60
ctgagatgct ctcctaagtc tgggcatgac actgtgtcct ggtaccaaca ggccctgggt 120
cagggggcccc agtttatctt tcagtattat gagggaggaag agagacagag aggcaacttc 180
cctgatcgat tctcaggtca ccagttccct aactatacgct ctgagctgaa tgtgaacgcc 240
ttgttgctgg gggactcggc cctcttatctc tgtgccagca gcttgg 286

<210> SEQ ID NO 95
<211> LENGTH: 286
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic

-continued

polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV5-7*01

<400> SEQUENCE: 95

gacgctggag tcacccaaag tcccacacac ctgatcaaaa cgagaggaca gcacgtgact	60
ctgagatgt ctcstatctc tgggcacacc agtgtgtcct cgtaccaaca ggccctgggt	120
caggggcccc agtttatctt tcagtattat gagaaagaag agagaggaag aggaaacttc	180
cctgatcaat tctcaggta ccagttccct aactatacgct ctgagctgaa tgtgaacgcc	240
ttgttgctag gggactcgcc cctctatctc tgtgccagca gcttgg	286

<210> SEQ ID NO 96
<211> LENGTH: 286
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV5-8*01

<400> SEQUENCE: 96

gagggctggag tcacacaaag tcccacacac ctgatcaaaa cgagaggaca gcaagcgact	60
ctgagatgt ctcstatctc tgggcacacc agtgtgtact ggtaccaaca ggccctgggt	120
ctgggectcc agttctctct ttggtatgac gagggtaag agagaaacag aggaaacttc	180
cctcctagat ttcaggtcg ccagttccct aattatacgct ctgagctgaa tgtgaacgcc	240
ttggagctgg aggactcgcc cctgtatctc tgtgccagca gcttgg	286

<210> SEQ ID NO 97
<211> LENGTH: 238
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV5-8*02

<400> SEQUENCE: 97

aggacagcaa gcgactctga gatgctctcc tatctctggg cacaccagtg tgtactggta	60
ccaacaggcc ctgggtctgg gcctccagct ctcctttgg tatgacgagg gtgaagagag	120
aaacagagga aactccctc cttagtttc aggtcgccag ttccctaatt atagctctga	180
gtgaatgtg aacgecttgg agctggagga ctggccctg tatctctgtg ccagcagc	238

<210> SEQ ID NO 98
<211> LENGTH: 287
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV6-1*01

<400> SEQUENCE: 98

aatgctggtg tcactcagac cccaaaattc caggtcctga agacaggaca gagcatgaca	60
ctgcagtgtg cccaggatat gaaccataac tccatgtact ggtatcgaca agacccaggc	120
atgggactga ggctgattta ttactcagct tctgagggtt ccactgacaa aggagaagtc	180

-continued

cccaatggct acaatgtctc cagattaaac aaacgggagt ttcgtcgatcg gctggagtcg	240
gctgctccct cccagacatc tgtgtacttc tgtgccagca gtgaagc	287

<210> SEQ ID NO 99
<211> LENGTH: 287
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV6-2*01

<400> SEQUENCE: 99

aatgctggtg tcactcagac cccaaaattc cgggtcctga agacaggaca gagcatgaca	60
ctgctgtgtg cccaggatat gaaccatgaa tacatgtact ggtatcgaca agacccaggc	120
atggggctga ggctgattca ttactcagtt ggtgagggtt caactgccaa aggagaggc	180
cctgatggct acaatgtctc cagattaaaa aaacagaatt ttcgtctgg gttggagtcg	240
gtctgctccct cccaaacatc tgtgtacttc tgtgccagca gttactc	287

<210> SEQ ID NO 100
<211> LENGTH: 287
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV6-3*01

<400> SEQUENCE: 100

aatgctggtg tcactcagac cccaaaattc cgggtcctga agacaggaca gagcatgaca	60
ctgctgtgtg cccaggatat gaaccatgaa tacatgtact ggtatcgaca agacccaggc	120
atggggctga ggctgattca ttactcagtt ggtgagggtt caactgccaa aggagaggc	180
cctgatggct acaatgtctc cagattaaaa aaacagaatt ttcgtctgg gttggagtcg	240
gtctgctccct cccaaacatc tgtgtacttc tgtgccagca gttactc	287

<210> SEQ ID NO 101
<211> LENGTH: 287
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV6-4*01

<400> SEQUENCE: 101

attgctggta tcacccaggc accaacatct cagatcctgg cagcaggacg gcgcatgaca	60
ctgagatgtt cccaggatat gagacataat gccatgtact ggtatagaca agatcttaga	120
ctggggctaa ggctcatcca ttattcaat actgcaggtt ccactggcaa aggagaagtc	180
cctgatggtt atagtgtctc cagagcaac acagatgatt tccccctcac gttggcgct	240
gtctgtaaccct ctcagacatc tgtgtacttc tgtgccagca gtgactc	287

<210> SEQ ID NO 102
<211> LENGTH: 287
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

-continued

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<220> FEATURE:

<223> OTHER INFORMATION: TRBV6-4*02

<400> SEQUENCE: 102

actgctggga tcacccaggc accaacatct cagatcctgg cagcaggacg gagcatgaca	60
ctgagatgta cccaggatat gagacataat gccatgtact ggtatagaca agatcttaga	120
ctggggctaa ggctcatcca ttattcaa atctgcaggtt ccactggcaa aggagaagtc	180
cctgatggtt atagtgtctc cagagcaac acagatgatt tccccctcac gttggcgct	240
gtgttaccct ctcagacatc tgtgtacttc tgtgccagca gtgactc	287

<210> SEQ ID NO 103

<211> LENGTH: 287

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<220> FEATURE:

<223> OTHER INFORMATION: TRBV6-5*01

<400> SEQUENCE: 103

aatgctggtg tcactcagac cccaaaattc caggtcctga agacaggaca gagcatgaca	60
ctgcagtgtg cccaggatat gaaccatgaa tacatgtctt ggtatcgaca agacccaggc	120
atggggctga ggctgattca ttactcagtt ggtgctggta tcactgacca aggagaagtc	180
cccaatggct acaatgtctc cagatcaacc acagaggatt tcccgtcag gctgctgtcg	240
gctgctccct cccagacatc tgtgtacttc tgtgccagca gttactc	287

<210> SEQ ID NO 104

<211> LENGTH: 287

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<220> FEATURE:

<223> OTHER INFORMATION: TRBV6-6*01

<400> SEQUENCE: 104

aatgctggtg tcactcagac cccaaaattc cgcatcctga agataggaca gagcatgaca	60
ctgcagtgtg cccaggatat gaaccataac tacatgtact ggtatcgaca agacccaggc	120
atggggctga agctgattta ttattcagtt ggtgctggta tcactgataa aggagaagtc	180
ccgaatggct acaacgtctc cagatcaacc acagaggatt tcccgtcag gctggagttg	240
gctgctccct cccagacatc tgtgtacttc tgtgccagca gttactc	287

<210> SEQ ID NO 105

<211> LENGTH: 282

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<220> FEATURE:

<223> OTHER INFORMATION: TRBV6-6*02

<400> SEQUENCE: 105

aatgctggtg tcactcagac cccaaaattc cgcatcctga agataggaca gagcatgaca	60
ctgcagtgtg cccaggatat gaaccataac tacatgtact ggtatcgaca agacccaggc	120

-continued

atggggctga agctgattta ttattcagtt ggtgctggta tcactgacaa aggagaagtc	180
ccgaatggct acaacgtctc cagatcaacc acagaggatt tcccgetcag gctggagttg	240
gctgctccct cccagacatc tgtgtacttc tgtgccagca gt	282

<210> SEQ ID NO 106
<211> LENGTH: 282
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV6-6*03

<400> SEQUENCE: 106	
aatgctggtg tcactcagac cccaaaattc cgcatcctga agataggaca gagcatgaca	60
ctgcagtgtg cccaggatat gaaccataac tacatgtact ggtatcgaca agaccaggc	120
atggggctga agctgattta ttattcagtt ggtgctggta tcactgataa aggagaagtc	180
ccgaatggct acaacgtctc cagatcaacc acagaggatt tcccgetcag gctggagttg	240
gctgctccct cccagacatc tgtgtacttc tgtgccagca gt	282

<210> SEQ ID NO 107
<211> LENGTH: 285
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV6-6*04

<400> SEQUENCE: 107	
aatgctggtg tcactcagac cccaaaattc cgcatcctga agataggaca gagcatgaca	60
ctgcagtgtg cccaggatat gaaccatgaa tacatgtact ggtatcgaca agaccaggc	120
atggggctga agctgattta ttattcagtt ggtgctggta tcactgataa aggagaagtc	180
ccgaatggct acaatgtctc cagatcaacc acagaggatt tcccgetcag gctggagttg	240
gctgctccct cccagacatc tgtgtacttc tgtgccagca gtcga	285

<210> SEQ ID NO 108
<211> LENGTH: 282
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV6-6*05

<400> SEQUENCE: 108	
aatgctggtg tcactcagac cccaaaattc cgcatcctga agataggaca gagcatgaca	60
ctgcagtgtg cccaggatat gaaccataac tacatgtact ggtatcgaca agaccaggc	120
atggggctga agctgattta ttattcagtt ggtgctggta tcactgacaa aggagaagtc	180
ccgaatggct acaacgtctc cagatcaacc acagaggatt tcccgetcag gctggagttg	240
gctgctccct cccagacatc tgtgtacttc tgtgccagca gc	282

<210> SEQ ID NO 109
<211> LENGTH: 287

-continued

<212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
 <220> FEATURE:
 <223> OTHER INFORMATION: TRBV6-7*01

<400> SEQUENCE: 109

aatgctggtg tcactcagac cccaaaattc cacgtcctga agacaggaca gagcatgact	60
ctgctgtgtg cccaggatat gaaccatgaa tacatgtatc ggtatcgaca agacccaggc	120
aaggggctga ggctgattt ctactcagtt gctgctgctc tcactgacaa aggagaagtt	180
cccaatggct acaatgtctc cagatcaaac acagaggatt tccccctcaa gctggagtca	240
gctgctccct ctcagacttc tgtttacttc tgtgccagca gttactc	287

<210> SEQ ID NO 110
 <211> LENGTH: 284
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
 <220> FEATURE:
 <223> OTHER INFORMATION: TRBV6-8*01

<400> SEQUENCE: 110

aatgctggtg tcactcagac cccaaaattc cacatcctga agacaggaca gagcatgaca	60
ctgcagtgtg cccaggatat gaaccatgga tacatgtctc ggtatcgaca agacccaggc	120
atggggctga gactgattt ctactcagct gctgctggta ctactgacaa agaagtcccc	180
aatggctaca atgtctctag attaacaca gaggattcc cactcaggct ggtgtcggt	240
gctccctccc agacatctgt gtacttgtt gccagcagtt actc	284

<210> SEQ ID NO 111
 <211> LENGTH: 287
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
 <220> FEATURE:
 <223> OTHER INFORMATION: TRBV6-9*01

<400> SEQUENCE: 111

aatgctggtg tcactcagac cccaaaattc cacatcctga agacaggaca gagcatgaca	60
ctgcagtgtg cccaggatat gaaccatgga tacttgtctc ggtatcgaca agacccaggc	120
atggggctga ggcgcattca ttactcagtt gctgctggta tcactgacaa aggagaagtc	180
cccgatggct acaatgtatc cagatcaaac acagaggatt tccccctca gctggagtca	240
gctgctccct cccagacatc tgtatacttc tgtgccagca gttattc	287

<210> SEQ ID NO 112
 <211> LENGTH: 290
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
 <220> FEATURE:
 <223> OTHER INFORMATION: TRBV7-01*01

<400> SEQUENCE: 112

-continued

ggtgctggag tctcccagtc cctgagacac aaggtagcaa agaaggaaa ggatgttagct	60
ctcagatatg atccaaatttc aggtcataat gcccttatt ggtaccgaca gagcctgggg	120
cagggectgg agtttcaat ttacttcaa ggcaaggatg caccagacaa atcggggct	180
ccccgtgatc gtttctctgc acagaggct gaggatcca tctccactct gaagttccag	240
cgcacacagc aggaggactt ggctgttat ctctgtgcca gcagctcagc	290

<210> SEQ ID NO 113
<211> LENGTH: 290
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV7-2*01

<400> SEQUENCE: 113

ggagctggag tctcccagtc ccccaagtaac aaggcacag agaaggaaa ggatgttagag	60
ctcaggtgtg atccaaatttc aggtcataact gcccttact ggtaccgaca gagcctgggg	120
cagggectgg agttttaat ttacttcaa ggcaacagtg caccagacaa atcagggtcg	180
cccaagtatc gtttctctgc agagaggact gggggatccg tctccactct gacgatccag	240
cgcacacagc aggaggactc ggccgtgtat ctctgtgcca gcagcttagc	290

<210> SEQ ID NO 114
<211> LENGTH: 290
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV7-2*02

<400> SEQUENCE: 114

ggagctggag tctcccagtc ccccaagtaac aaggcacag agaaggaaa ggatgttagag	60
ctcaggtgtg atccaaatttc aggtcataact gcccttact ggtaccgaca gagcctgggg	120
cagggectgg agttttaat ttacttcaa ggcaacagtg caccagacaa atcagggtcg	180
cccaagtatc gtttctctgc agagaggact ggggaatccg tctccactct gacgatccag	240
cgcacacagc aggaggactc ggccgtgtat ctctgtgcca gcagcttagc	290

<210> SEQ ID NO 115
<211> LENGTH: 290
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV7-2*03

<400> SEQUENCE: 115

ggagctggag tctcccagtc ccccaagtaac aaggcacag agaaggaaa ggatgttagag	60
ctcaggtgtg atccaaatttc aggtcataact gcccttact ggtaccgaca gagcctgggg	120
cagggectgg agttttaat ttacttcaa ggcaacagtg caccagacaa atcagggtcg	180
cccaagtatc gtttctctgc agagaggact ggggaatccg tctccactct gacgatccag	240
cgcacacagc aggaggactc ggccgtgtat ctctgtacca gcagcttagc	290

<210> SEQ ID NO 116
<211> LENGTH: 288
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV7-2*04

<400> SEQUENCE: 116

```
ggagctggag tttccagtc ccccgtaac aaggcacag agaaggaaa ggatgttagag      60
ctcagggtgt atccaatttc aggtcataact gcccattact ggtaccgaca gagcctgggg    120
cagggcctgg agttttaat ttacttcaa ggcaacagtg caccagacaa atcagggctg    180
cccaacgtatc gtttctgtgc agagaggact gggggatccg tctccactt gacgatccag    240
cgcacacacgc aggaggactc ggccgtgtat ctctgtgcca gcagctta                      288
```

<210> SEQ ID NO 117
<211> LENGTH: 290
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV7-3*01

<400> SEQUENCE: 117

```
ggtgctggag tctccagac ccccgtaac aaggcacag agaaggaaa atatgttagag      60
ctcagggtgt atccaatttc aggtcataact gcccattact ggtaccgaca aagcctgggg    120
cagggcctgg agttttaat ttacttcaa ggacgggtt cggcagatga ctcagggctg    180
cccaacgtatc gtttctgtgc agtcaggcct gagggatccg tctctactt gaagatccag    240
cgcacacacgc gggggactc agccgtgtat ctctgtgcca gcagcttaac                      290
```

<210> SEQ ID NO 118
<211> LENGTH: 290
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV7-3*02

<400> SEQUENCE: 118

```
ggtgctggag tctccagac ccccgtaac aaggcacag agaaggaaa agatgttagag      60
ctcagggtgt atccaatttc aggtcataact gcccattact ggtaccgaca aagcctgggg    120
cagggcctgg agttttaat ttacttcaa ggacgggtt cggcagatga ctcagggctg    180
cccaaaagatc gtttctgtgc agtcaggcct gagggatccg tctctactt gaagatccag    240
cgcacacacgc gggggactc agccgtgtat ctccgtgcca gcagcttaac                      290
```

<210> SEQ ID NO 119
<211> LENGTH: 288
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV7-3*03

-continued

<400> SEQUENCE: 119

```

ggtgctggag tctccagac ccccagtaac aaggcacag agaaggaaa agatgttagag      60
ctcaggtgtg atccaatttc aggtcataact gcccttact ggtaccgaca aagcctgggg     120
cagggcccg agtttctaatttccaa ggcacgggtg cggcagatga ctcaggctg             180
cccaaaagatc ggttcttgc agtcaggcct gagggatccg tctctactct gaagatccag     240
cgcacagagc agggggactc agccgcgtat ctctgtgcca gcagctta                  288

```

<210> SEQ ID NO 120

<211> LENGTH: 285

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<220> FEATURE:

<223> OTHER INFORMATION: TRBV7-3*04

<400> SEQUENCE: 120

```

ggtgctggag tctccagac ccccagtaac aaggcacag agaaggaaa atatgttagag      60
ctcaggtgtg atccaatttc aggtcataact gcccttact ggtaccgaca aagcctgggg     120
cagggcccg agtttctaatttccaa ggcacgggtg cggcagatga ctcaggctg             180
cccaacgatc ggttcttgc agtcaggcct gagggatccg tctctactct gaagatccag     240
cgcacagagc gggggactc tgccgtgtat ctctgtgcca gcagc                         285

```

<210> SEQ ID NO 121

<211> LENGTH: 231

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<220> FEATURE:

<223> OTHER INFORMATION: TRBV7-3*05

<400> SEQUENCE: 121

```

tgggagctca ggtgtatcc aatttcaggtaactgtcccc ttactggta ccgacaaagc      60
ctggggcagg gcccagagct tctaaatttac ttccaaaggca cgggtgcggc agatgactca    120
gggctgcccc acgatcggtt ctgtcaggta aggcctgagg gatccgtctc tactctgaag    180
atccagcgca cagagcgggg ggactcagcc gtgtatctc gtgccagcagc c                   231

```

<210> SEQ ID NO 122

<211> LENGTH: 290

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<220> FEATURE:

<223> OTHER INFORMATION: TRBV7-4*01

<400> SEQUENCE: 122

```

ggtgctggag tctccagtc cccaaaggtaac aaagtgc当地 agagggacg ggatgttagct      60
ctcaggtgtg attcaatttc gggcatgtta acccttattt ggtaccgaca gaccctgggg     120
cagggctcg aggttctgac ttactcccg agtgcgtc aacgagacaa atcaggccgg             180
cccaaggtaac gggtctctgc agagaggcct gagagatccg tctccactct gaagatccag     240
cgcacagagc agggggactc agctgtgtat ctctgtgcca gcagcttagc                  290

```

-continued

<210> SEQ_ID NO 123
<211> LENGTH: 288
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV7-5*01

<400> SEQUENCE: 123

ggtgctggag tctccaggc cccaaaggac gaagtcaac agaggggaca ggatgttagct	60
cccagggtgtg atccaatttc gggtcaggta accctttatt ggtaccgaca gaccctgggg	120
cagggccaag agtttctgac ttcccttccag gatgaaactc aacaagataa atcagggtcg	180
ctcagtgtac aattctccac agagaggct gaggatctt ctccacactga agatccagcg	240
cacagagcaa gggcgactcg gctgtgtatc tctgtgccag aagcttag	288

<210> SEQ_ID NO 124
<211> LENGTH: 289
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV7-5*02

<400> SEQUENCE: 124

ggtgctggag tctccaggc cccaaaggac gaagtcaac agaggggaca ggatgttagct	60
cccagggtgtg atccaatttc gggtcaggta accctttatt ggtaccgaca gaccctgggg	120
cagggccaag agtttctgac ttcccttccag gatgaaactc aacaagataa atcagggtcg	180
ctcagtgtac aattctccac agagaggct gaggatctt ctccacactga agatccagcg	240
cacagagcaa gggcgactcg gctgtgtatc tctgtgtcag aagcttag	289

<210> SEQ_ID NO 125
<211> LENGTH: 290
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV7-6*01

<400> SEQUENCE: 125

ggtgctggag tctccaggc tcccaaggac aaagtcaac agaggggaca ggatgttagct	60
ctcagggtgtg atccaatttc gggtcatgtt tccctttatt ggtaccgaca ggccctgggg	120
cagggcccaag agtttctgac ttacttcaat tatgaagccc aacaagacaa atcagggtcg	180
cccaatgtac gtttctctgc agagaggct gagggatcca tctccactct gacgtccag	240
cgcacagagc agcgggactc ggccatgtat cgctgtgccat gcagcttagc	290

<210> SEQ_ID NO 126
<211> LENGTH: 285
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:

-continued

<223> OTHER INFORMATION: TRBV7-6*02

<400> SEQUENCE: 126

ggtgctggag tctccaggta	aaagtacaaa agaggggaca	ggatgttagct	60	
ctcaggtgtg atccaatctc	gggtcatgta	tcccttatt ggtaccgaca	ggccctgggg	120
cagggccag agtttctgac	ttacttcaat tatgaagccc	aacaagacaa atcaggctg	180	
cccaatgatc ggttctctgc	agagaggct gagggatcca	tctccactct gacgatccag	240	
cgcacagagc	agcgggactc ggccatgtat	cgctgtgcca gcagc	285	

<210> SEQ ID NO 127

<211> LENGTH: 290

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<220> FEATURE:

<223> OTHER INFORMATION: TRBV7-7*01

<400> SEQUENCE: 127

ggtgctggag tctccaggta	aaagtacaaa agaggggaca	ggatgttaact	60	
ctcaggtgtg atccaatttc	gagtcatgca	acccttatt ggtatcaaca	ggccctgggg	120
cagggccag agtttctgac	ttacttcaat tatgaagctc	aaccagacaa atcaggctg	180	
cccagtgtatc ggttctctgc	agagaggct gagggatcca	tctccactct gacgattcag	240	
cgcacagagc	agcgggactc agccatgtat	cgctgtgcca gcagcttgc	290	

<210> SEQ ID NO 128

<211> LENGTH: 285

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<220> FEATURE:

<223> OTHER INFORMATION: TRBV7-7*02

<400> SEQUENCE: 128

ggtgctggag tctccaggta	aaagtacaaa agaggggaca	ggatgttaact	60	
ctcaggtgtg atccaatttc	gagtcatgta	acccttatt ggtatcaaca	ggccctgggg	120
cagggccag agtttctgac	ttacttcaat tatgaagctc	aaccagacaa atcaggctg	180	
cccagtgtatc ggttctctgc	agagaggct gagggatcca	tctccactct gacgattcag	240	
cgcacagagc	agcgggactc agccatgtat	cgctgtgcca gcagc	285	

<210> SEQ ID NO 129

<211> LENGTH: 290

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<220> FEATURE:

<223> OTHER INFORMATION: TRBV7-8*01

<400> SEQUENCE: 129

ggtgctggag tctccaggta	aaagtgcata agagaggaca	ggatgttagct	60	
ctcaggtgtg atccaatttc	gggtcatgta	tccctttttt ggtaccaaca	ggccctgggg	120
cagggccag agtttctgac	ttatccatcg	aatgaagctc aactagacaa	atcggggctg	180

-continued

cccaagtgtac gcttctttgc agaaaaggcct gagggatccg tctccactct gaagatccag 240

cgcacacacgc aggaggactc cgccgtgtat ctctgtgcca gcagcttagc 290

<210> SEQ ID NO 130

<211> LENGTH: 290

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<220> FEATURE:

<223> OTHER INFORMATION: TRBV7-8*02

<400> SEQUENCE: 130

ggtgctggag tctcccagtc ccctaggtac aaagtgcaca agagaggaca ggatgtagct 60

ctcaggtgtg atccaaatttc gggcatgtta tccctttttt ggtaccaaca ggccctgggg 120

cagggggccag agtttctgac ttatttccag aatgaagctc aactagacaa atcggggctg 180

cccaagtgtac gcttctttgc agaaaaggcct gagggatccg tctccactct gaagatccag 240

cgcacacacgc aggaggactc cgccgtgtat ctctgtgcca gcagcttagc 290

<210> SEQ ID NO 131

<211> LENGTH: 288

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<220> FEATURE:

<223> OTHER INFORMATION: TRBV7-8*03

<400> SEQUENCE: 131

ggtgctggag tctcccagtc ccctaggtac aaagtgcaca agagaggaca ggatgtagct 60

ctcaggtgtg atccaaatttc gggcatgtta tccctttttt ggtaccaaca ggccctgggg 120

cagggggccag agtttctgac ttatttccag aatgaagctc aactagacaa atcggggctg 180

cccaagtgtac gcttctttgc agaaaaggcct gagggatccg tctccactct gaagatccag 240

cgcacacacgc aggaggactc cgccgtgtat ctctgtgcca gcagccga 288

<210> SEQ ID NO 132

<211> LENGTH: 288

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<220> FEATURE:

<223> OTHER INFORMATION: TRBV7-9*05

<400> SEQUENCE: 132

gatactggag tctcccagaa cccccagacac aagatcacaa agaggggaca gaatgttaact 60

ttcaggtgtg atccaaatttc tgaacacaac cgcccttattt ggtacccaca gaccctgggg 120

cagggggccag agtttctgac ttacttccag aatgaagctc aactagaaaa atcaaggctg 180

cccaagtgtac gtttctctgc agagaggcct aagggatctc totccaccc ttggagatccag 240

cgcacacacgc agggggactc ggccatgtat ctctgtgcca gcaccaaa 288

<210> SEQ ID NO 133

<211> LENGTH: 288

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

-continued

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV7-9*06

<400> SEQUENCE: 133

gatactggag tctcccagaa ccccagacac aagatcacaa agaggggaca gaatgtact	60
ttcaggtgtg atccaatattc tgaacacaac cgcccttatt ggtaccgaca gaccctgggg	120
cagggcccaag agtttctgac ttacttccag aatgaagctc aactagaaaa atcaaggctg	180
ctcagtgate ggttctctgc agagaggct aagggatctc tttccacctt ggagatccag	240
cgcacagagc agggggactc ggccatgtat ctctgtgccca gcacgttg	288

<210> SEQ ID NO 134
<211> LENGTH: 285
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV7-9*03

<400> SEQUENCE: 134

gatactggag tctcccagga ccccagacac aagatcacaa agaggggaca gaatgtact	60
ttcaggtgtg atccaatattc tgaacacaac cgcccttatt ggtaccgaca gaccctgggg	120
cagggcccaag agtttctgac ttacttccag aatgaagctc aactagaaaa atcaaggctg	180
ctcagtgate ggttctctgc agagaggct aagggatctt tttccacctt ggagatccag	240
cgcacagagc agggggactc ggccatgtat ctctgtgccca gcacgttg	285

<210> SEQ ID NO 135
<211> LENGTH: 290
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV7-9*01

<400> SEQUENCE: 135

gatactggag tctcccagaa ccccagacac aagatcacaa agaggggaca gaatgtact	60
ttcaggtgtg atccaatattc tgaacacaac cgcccttatt ggtaccgaca gaccctgggg	120
cagggcccaag agtttctgac ttacttccag aatgaagctc aactagaaaa atcaaggctg	180
ctcagtgate ggttctctgc agagaggct aagggatctt tttccacctt ggagatccag	240
cgcacagagc agggggactc ggccatgtat ctctgtgccca gcacgttagc	290

<210> SEQ ID NO 136
<211> LENGTH: 288
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV7-9*02

<400> SEQUENCE: 136

gatactggag tctcccagaa ccccagacac aacatcacaa agaggggaca gaatgtact	60
ttcaggtgtg atccaatattc tgaacacaac cgcccttatt ggtaccgaca gaccctgggg	120

-continued

cagggcccg agtttctgac ttacttccag aatgaagctc aactagaaaa atcaaggctg	180
ctcagtgatc gtttctctgc agagaggcct aaggatctt tctccaccc ggagatccag	240
cgcacagagc agggggactc ggccatgtat ctctgtgccca gcagctta	288
<210> SEQ ID NO 137	
<211> LENGTH: 207	
<212> TYPE: DNA	
<213> ORGANISM: Artificial Sequence	
<220> FEATURE:	
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide	
<220> FEATURE:	
<223> OTHER INFORMATION: TRBV7-9*07	
<400> SEQUENCE: 137	
cacaaccggcc tttattggta ccgacagacc ctggggcagg gcccagagg ttctgacttac	60
ttccagaatg aagctcaact agaaaaatca aggctgtca gtgategggtt ctctgcagag	120
aggcctaagg gatctttctc cacttggag atccagcgca cagaggaggg ggactcgccc	180
atgttatctct gtgccagcag cagcagt	207
<210> SEQ ID NO 138	
<211> LENGTH: 288	
<212> TYPE: DNA	
<213> ORGANISM: Artificial Sequence	
<220> FEATURE:	
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide	
<220> FEATURE:	
<223> OTHER INFORMATION: TRBV7-9*04	
<400> SEQUENCE: 138	
atatctggag tctcccacaa cccagacac aagatcacaa agaggggaca gaatgtact	60
ttcaggtgtg atccaaatttc tgaacacaac cgcccttatt ggtaccgaca gaaccctggg	120
cagggcccg agtttctgac ttacttccag aatgaagctc aactggaaaa atcaggctg	180
ctcagtgatc ggtatctctgc agagaggcct aaggatctt tctccaccc ggagatccag	240
cgcacagagc agggggactc ggccatgtat ctctgtgccca gcagctct	288
<210> SEQ ID NO 139	
<211> LENGTH: 279	
<212> TYPE: DNA	
<213> ORGANISM: Artificial Sequence	
<220> FEATURE:	
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide	
<220> FEATURE:	
<223> OTHER INFORMATION: TRBV8-1*01	
<400> SEQUENCE: 139	
gaggcaggga tcagccagat accaagatata cacagacaca cagggaaaaa gatcatcctg	60
aaatatgctc agataggaa ccattattca gtgttctgtt atcaataaga ccaagaataag	120
gggctgaggc tgatccatta ttccaggtgtt attggcagca tgaccaaagg cggtgccaaag	180
gaagggtaca atgtctctgg aaacaagctc aagcattttc cctcaaccct ggagtctact	240
agcaccagcc agacctctgtt acctctgtgg cagtgcatc	279
<210> SEQ ID NO 140	
<211> LENGTH: 271	
<212> TYPE: DNA	
<213> ORGANISM: Artificial Sequence	

-continued

<220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV8-2*01

<400> SEQUENCE: 140

gatgctggaa tcacccagat gccaagatatacattgtac agaagaaga gatgatctg	60
gaatgtgctc aggttaggaa cagtgttctg atatcgacag gaccaagac gggggctgaa	120
gcttatccac tattcaggca gtggtcacag caggacaaa gttgatgtca cagagggta	180
ctgtgtttct tgaaaacaagc ttgagcattt ccccaatcct ggcattacc accgaccagcc	240
agacctatct gtaccactgt ggcagcacat c	271

<210> SEQ ID NO 141
 <211> LENGTH: 286
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV9*01

<400> SEQUENCE: 141

gattctggag tcacacaaaac cccaaaggac ctgatcacag caactggaca gcgagtgacg	60
ctgagatgct cccctaggc tggagacctc tctgtgtact ggtaccaaca gagcctggac	120
cagggectcc agttcctcat tcagttttat aatggagaag agagagcaa aggaaacatt	180
cttgaacgat tctccgcaca acagttccct gacttgcact ctgaactaaa cctgagctct	240
ctggagctgg gggactcage tttgtatttc tgtgccagca gcgttag	286

<210> SEQ ID NO 142
 <211> LENGTH: 282
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV9*03

<400> SEQUENCE: 142

gattctggag tcacacaaaac cccaaaggac ctgatcacag caactggaca gcgagtgacg	60
ctgagatgct cccctaggc tggagacctc tctgtgtact ggtaccaaca gagcctggac	120
cagggectcc agttcctcat tcaatatttt aatggagaag agagagcaa aggaaacatt	180
cttgaacgat tctccgcaca acagttccct gacttgcact ctgaactaaa cctgagctct	240
ctggagctgg gggactcage tttgtatttc tgtgccagca gc	282

<210> SEQ ID NO 143
 <211> LENGTH: 286
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV9*02

<400> SEQUENCE: 143

gattctggag tcacacaaaac cccaaaggac ctgatcacag caactggaca gcgagtgacg	60
--	----

-continued

ctgagatgct cccctaggc tggagaccc tctgtgtact ggtaccaaca gagcctggac	120
cagggcctcc agtttctcat tcactattat aatggagaag agagagcaaa aggaaacatt	180
cttgaacgat tctccgcaca acagttccct gacttgact ctgaactaaa cctgagctct	240
ctggagctgg gggactcagc tttgtatttc tgtgccagca gttagtc	286

<210> SEQ ID NO 144
<211> LENGTH: 287
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV10-1*01

<400> SEQUENCE: 144

gatgctgaaa tcacccagag cccaagacac aagatcacag agacaggaag gcaggtgacc	60
ttggcgtgtc accagacttg gaaccacaac aatatgttct ggtatcgaca agacctggga	120
catgggctga ggctgatcca ttactcatat ggtgttcaag acactaacaa aggagaagtc	180
tcagatggct acagtgtctc tagatcaaac acagaggacc tccccctcac tctggagtc	240
gtgcctcct cccagacatc tgtatatttc tgccgcagca gttagtc	287

<210> SEQ ID NO 145
<211> LENGTH: 282
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV10-1*02

<400> SEQUENCE: 145

gatgctgaaa tcacccagag cccaagacac aagatcacag agacaggaag gcaggtgacc	60
ttggcgtgtc accagacttg gaaccacaac aatatgttct ggtatcgaca agacctggga	120
catgggctga ggctgatcca ttactcatat ggtgttcaag acactaacaa aggagaagtc	180
tcagatggct acagtgtctc tagatcaaac acagaggacc tccccctcac tctggagtc	240
gtgcctcct cccagacatc tgtatatttc tgccgcagca gttagtc	282

<210> SEQ ID NO 146
<211> LENGTH: 287
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV10-2*01

<400> SEQUENCE: 146

gatgctggaa tcacccagag cccaagatac aagatcacag agacaggaag gcaggtgacc	60
ttgatgtgtc accagacttg gagccacagc tatatgttct ggtatcgaca agacctggga	120
catgggctga ggctgatcta ttactcagca gctgctgata ttacagataa aggagaagtc	180
cccgatggct atgttgtctc cagatccaag acagagaatt tccccctcac tctggagtc	240
gttacccgct cccagacatc tgtgtatttc tgccgcagca gttagtc	287

<210> SEQ ID NO 147

-continued

<211> LENGTH: 217
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV10-2*02

<400> SEQUENCE: 147

aaggcaggtg accttgatgt gtcaccagac ttggagccac agctataatgt tctggtatcg	60
acaagacctg ggacatgggc tgaggctgtat ctattactca gcagctgctg atattacaga	120
taaaggagaa gtccccatgt gctacgttgtt ctccagatcc aagacagaga atttccccct	180
cactctggag tcagctaccc gctcccgacat atctgtg	217

<210> SEQ ID NO 148
<211> LENGTH: 273
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV10-3*03

<400> SEQUENCE: 148

gatgctggaa tcacccagag cccaagacac aaggtcacag agacaggaac accagtgact	60
ctgagatgtc accagactga gaaccaccgc tacatgtact ggtatcgaca agacccgggg	120
catgggctga ggctaatcca ttactcatat ggtgttaaag atactgacaa aggagaagtc	180
tcagatggct atagtgtctc tagatcaaag acagaggatt tcctcctcac tctggagtcc	240
gctaccagct cccagacatc tgtgtacttc tgt	273

<210> SEQ ID NO 149
<211> LENGTH: 273
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV10-3*04

<400> SEQUENCE: 149

gatgctggaa tcacccagag cccaagacac aaggtcacag agacaggaac accagtgact	60
ctgagatgtc accagactga gaaccaccgc tacatgtact ggtatcgaca agacccgggg	120
catgggctga ggctaatcca ttactcatat ggtgttaaag atactgacaa aggagaagtc	180
tcagatggct atagtgtctc tagatcaaag acagaggatt tcctcctcac tctggagtcc	240
gctaccagct cccagacatc tgtgtacttc tgt	273

<210> SEQ ID NO 150
<211> LENGTH: 287
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV10-3*01

<400> SEQUENCE: 150

gatgctggaa tcacccagag cccaagacac aaggtcacag agacaggaac accagtgact	60
---	----

-continued

ctgagatgtc accagactga gaaccaccgc tataatgtact ggtatcgaca agacccgggg 120
 catgggctga ggctgtatcca ttactcatat ggtgttaaag atactgacaa aggagaagtc 180
 tcagatggct atagtgtctc tagatcaaag acagaggatt tcctcctcac tctggagtc 240
 gctaccagct cccagacatc tgtgtacttc tgtgccatca gtgagtc 287

<210> SEQ ID NO 151
 <211> LENGTH: 287
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
 <220> FEATURE:
 <223> OTHER INFORMATION: TRBV10-3*02

<400> SEQUENCE: 151
 gatgctggaa tcacccagag cccaaagacac aaggtaacag agacaggaac accagtgact 60
 ctgagatgtc atcagactga gaaccaccgc tataatgtact ggtatcgaca agacccgggg 120
 catgggctga ggctgtatcca ttactcatat ggtgttaaag atactgacaa aggagaagtc 180
 tcagatggct atagtgtctc tagatcaaag acagaggatt tcctcctcac tctggagtc 240
 gctaccagct cccagacatc tgtgtacttc tgtgccatca gtgagtc 287

<210> SEQ ID NO 152
 <211> LENGTH: 290
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
 <220> FEATURE:
 <223> OTHER INFORMATION: TRBV11-1*01

<400> SEQUENCE: 152
 gaagctgaag ttgcccagtc ccccgatata aagattacag agaaaaagcga ggctgtggct 60
 ttttggtgta atccttatttc tgcccatgtt accctttact ggtacccggca gatcctggga 120
 caggggcccg agcttctggt tcaatttcag gatgagatgt tagtagatga ttcacagttg 180
 cctaaggatc gatTTCTGC agagaggctc aaaggatgtt actccactct caagatccag 240
 cctgcagagc ttggggactc ggccatgtat ctctgtgcga gcagcttagc 290

<210> SEQ ID NO 153
 <211> LENGTH: 290
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
 <220> FEATURE:
 <223> OTHER INFORMATION: TRBV11-3*01

<400> SEQUENCE: 153
 gaagctggag tgggtcagtc tccccatata aagattatag agaaaaaaaca gcctgtggct 60
 ttttggtgca atccttatttc tgccacaat accctttact ggtacccgtca gaacttggga 120
 caggggcccg agcttctgtt tcgatatgtt aatgagatgtt cagtagacgtt ttcacagttg 180
 cctaaggatc gatTTCTGC agagaggctc aaaggatgtt actccactct caagatccag 240
 cctgcagagc ttggggactc ggccgtgtat ctctgtgcga gcagcttaga 290

-continued

<210> SEQ ID NO 154
<211> LENGTH: 285
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV11-3*02

<400> SEQUENCE: 154

```
gaagctggag tgggtcagtc tcccagatata gaggattat aaaaaaagca gcctgtggct      60
tttggtgca atccttatcc tggccacaat acccttact ggtaccggca gaacttggga      120
caggggccccgg agcttctgat tcgatatgag aatgaggaag cagtagacga ttcacagttg      180
cctaaggatc gatttctgc agagaggctc aaaggagtag actccactct caagatccag      240
cctgcagagc ttggggactc ggccgtgtat ctctgtgcca gcagc      285
```

<210> SEQ ID NO 155
<211> LENGTH: 269
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV11-3*03

<400> SEQUENCE: 155

```
ggtctcccg atataagatt atagagaaga aacagcctgt ggcttttgg tgcaatccaa      60
tttctggcca caataccctt tactggtacc tgcagaacctt gggacagggc ccggagcttc      120
tgattcata tgagaatgag gaagcagtag acgattcaca gttgcctaag gatcgatttt      180
ctgcagagag gctcaaagga gttagactcca ctctcaagat ccagccagca gagcttgggg      240
actcggccat gtatctctgt gccagcagc      269
```

<210> SEQ ID NO 156
<211> LENGTH: 290
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV11-2*01

<400> SEQUENCE: 156

```
gaagctggag ttgcccaagtc tcccagatata gaggattat aaaaaaggca gagtgtggct      60
tttggtgca atccttatcc tggccatgtc acccttact ggtaccagca gatctggga      120
caggggccaa agcttctgat tcagttcag aataacggtg tagtggatga ttcacagttg      180
cctaaggatc gatttctgc agagaggctc aaaggagtag actccactct caagatccag      240
cctgcaaagc ttgaggactc ggccgtgtat ctctgtgcca gcagcttaga      290
```

<210> SEQ ID NO 157
<211> LENGTH: 285
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV11-2*03

-continued

<400> SEQUENCE: 157

gaagctggag ttgcccatgc tcccgatata aagattata gaaaaaggca gagtgtggct	60
ttttgtgca atcctata tgcgcatgt acccttact ggtaccagca gatcctggaa	120
caggggccaa agcttctgat tcagtttcag aataacggtg tagtggatga ttcacagttg	180
cctaaggatc gatttctgc agagaggctc aaaggagtag actccactct caagatcaa	240
cctgcaaagc ttgaggactc ggccgtgtat ctctgtgcca gcagc	285

<210> SEQ ID NO 158

<211> LENGTH: 285

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<220> FEATURE:

<223> OTHER INFORMATION: TRBV11-2*02

<400> SEQUENCE: 158

gaagctggag ttgcccatgc tcccgatata aagattata gaaaaaggca gagtgtggct	60
ttttgtgca atcctata tgcgcatgt acccttact ggtaccagca gatcctggaa	120
caggggccaa agcttctgat tcagtttcag aataacggtg tagtggatga ttcacagttg	180
cctaaggatc gatttctgc agagaggctc aaaggagtag actccactct caagatccag	240
cctgcaaagc ttgagaactc ggccgtgtat ctctgtgcca gcagt	285

<210> SEQ ID NO 159

<211> LENGTH: 290

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<220> FEATURE:

<223> OTHER INFORMATION: TRBV12-1*01

<400> SEQUENCE: 159

gatgctggtg ttatccatgc acccaggcac aaagtgcac agatggaca atcagtaact	60
ctgagatgcg aaccaatttcc aggcacaaat gatcttctct ggtacagaca gacctttgt	120
cagggactgg aattgctgaa ttacttctgc agctggaccc tcgttagatga ctcaggagtg	180
tccaaggatt gattctcagc acagatgcct gatgtatcat tctccactct gaggatccag	240
cccatggAAC ccaggactt gggccttatat ttctgtgcca gcagctttgc	290

<210> SEQ ID NO 160

<211> LENGTH: 290

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<220> FEATURE:

<223> OTHER INFORMATION: TRBV12-2*01

<400> SEQUENCE: 160

gatgctggca ttatccatgc acccaagcat gaggtgcac agaatggaca aacagtgcact	60
ctgagatgtg agccaaatttcc aggcacaaat ttcccttctct ggtacagaga taccttcgt	120
cagggactgg aattgctgag ttacttccgg agctgatcta ttatagataa tgcaggatgt	180
cccacagagc gattctcagc tgagaggcct gatggatcat tctctactct gaagatccag	240

-continued

cctgcagagc agggggactc ggccgtgtat gtctgtcaa gtcgcttagc	290
---	-----

<210> SEQ ID NO 161
<211> LENGTH: 290
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV12-4*01

<400> SEQUENCE: 161

gatgctggag ttatccagtc accccggcac gaggtgacag agatggaca agaagtgact	60
ctgagatgta aaccaatttc aggacacgac tacctttct ggtacagaca gaccatgatg	120
cggggactgg agttgctcat ttactttaac aacaacgttc cgatagatga ttcagggatg	180
cccgaggatc gatttcagc taagatgcct aatgcatcat tctccactct gaagatccag	240
ccctcagaac ccagggactc agctgtgtac ttctgtgcca gcagtttagc	290

<210> SEQ ID NO 162
<211> LENGTH: 288
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV12-4*02

<400> SEQUENCE: 162

gatgctggag ttatccagtc accccggcac gaggtgacag agatggaca agaagtgact	60
ctgagatgta aaccaatttc aggacatgac tacctttct ggtacagaca gaccatgatg	120
cggggactgg agttgctcat ttactttaac aacaacgttc cgatagatga ttcagggatg	180
cccgaggatc gatttcagc taagatgcct aatgcatcat tctccactct gaggatccag	240
ccctcagaac ccagggactc agctgtgtac ttctgtgcca gcagttta	288

<210> SEQ ID NO 163
<211> LENGTH: 290
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV12-3*01

<400> SEQUENCE: 163

gatgctggag ttatccagtc accccggccat gaggtgacag agatggaca agaagtgact	60
ctgagatgta aaccaatttc aggcacacaac tccctttct ggtacagaca gaccatgatg	120
cggggactgg agttgctcat ttactttaac aacaacgttc cgatagatga ttcagggatg	180
cccgaggatc gatttcagc taagatgcct aatgcatcat tctccactct gaagatccag	240
ccctcagaac ccagggactc agctgtgtac ttctgtgcca gcagtttagc	290

<210> SEQ ID NO 164
<211> LENGTH: 290
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

-continued

<220> FEATURE:
<223> OTHER INFORMATION: TRBV12-5*01

<400> SEQUENCE: 164

```

gatgctagag tcacccagac accaaggcac aaggtagacag agatggaca agaagtaaca      60
atgagatgtc agccaatttt aggccacaat actgttttct ggtacagaca gaccatgtg      120
caaggactgg agttgtggc ttacttccgc aaccgggctc ctctagatga ttcggggatg      180
ccgaaggatc gattctcagc agagatgcct gatgcaactt tagccactt gaagatccag      240
ccctcagaac ccaggactc agctgtgtat ttttgtcta gtggtttggt                  290

```

<210> SEQ ID NO 165
<211> LENGTH: 287
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV12*01

<400> SEQUENCE: 165

```

gctgctggag tcatccagtc cccaagacat ctgatcaaag aaaagaggga aacagccact      60
ctgaaatgct atcctatccc tagacacgc acgtgtctact ggtaccagca gggtccagg      120
caggcccccc agttcctcat ttcgttttat gaaaagatgc agagcgataa aggaagcattc      180
cctgatcgat tctcagctca acagttcagt gactatcatt ctgaactgaa catgagctcc      240
ttggagctgg gggactcagc cctgtacttc tgtgccagca gcttagg                  287

```

<210> SEQ ID NO 166
<211> LENGTH: 282
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV13*02

<400> SEQUENCE: 166

```

gctgctggag tcateccagtc cccaagacat ctgatcagag aaaagaggga aacagccact      60
ctgaaatgct atcctatccc tagacacgc acgtgtctact ggtaccagca gggcccagg      120
caggcccccc agttcctcat ttcgttttat gaaaagatgc agagcgataa aggaagcattc      180
cctgatcgat tctcagctca acagttcagt gactatcatt ctgaactgaa catgagctcc      240
ttggagctgg gggactcagc cctgtacttc tgtgccagca gc                      282

```

<210> SEQ ID NO 167
<211> LENGTH: 290
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV14*01

<400> SEQUENCE: 167

```

gaagctggag ttactcagtt cccccagccac agcgtaatag agaaggccca gactgtgact      60
ctgagatgtc acccaatttc tggacatgtat aatctttat ggtatcgacg tgttatggg      120
aaagaaataa aatttctgtt acatTTTGTG aaagagtcta aacaggatga gtccggatg      180

```

-continued

cccaacaatc gattcttagc tgaaaggact ggagggacgt attctactct gaaggtgcag	240
cctgcagaac tggaggattc tggagtttat ttctgtgcca gcagccaaga	290

<210> SEQ ID NO 168
<211> LENGTH: 285
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV14*02

<400> SEQUENCE: 168

gaagctggag ttactcagtt ccccagccac agcgtaatag agaagggcca gactgtgact	60
ctgagatgtg acccaatttc tggacatgtat aatctttatt ggtatcgacg tgttatggga	120
aaagaataaa aatttctgtt acattttgtg aaagagtcta aacaggatga atccggatg	180
cccaacaatc gattcttagc tgaaaggact ggagggacgt attctactct gaaggtgcag	240
cctgcagaac tggaggattc tggagtttat ttctgtgcca gcagc	285

<210> SEQ ID NO 169
<211> LENGTH: 287
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV15*01

<400> SEQUENCE: 169

gatgccatgg tcatccagaa cccaagatac caggttaccc agtttgaaa gccagtgacc	60
ctgagttgtt ctcagacttt gaaccataac gtcatgtact ggtaccagca gaagtcaagt	120
caggccccaa agctgctgtt ccactactat gacaaagatt ttaacaatga agcagacacc	180
cctgataact tccaatccag gaggccgaac acttctttct gttttttaga catccgctca	240
ccaggectgg gggacacagc catgtacctg tgtgccacca gcagaga	287

<210> SEQ ID NO 170
<211> LENGTH: 282
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV15*03

<400> SEQUENCE: 170

gatgccatgg tcatccagaa cccaagatac cgggttaccc agtttgaaa gccagtgacc	60
ctgagttgtt ctcagacttt gaaccataac gtcatgtact ggtaccagca gaagtcaagt	120
caggccccaa agctgctgtt ccactactat aacaaagatt ttaacaatga agcagacacc	180
cctgataact tccaatccag gaggccgaac acttctttct gttttttaga catccgctca	240
ccaggectgg gggacacagc catgtacccatg tgtgccacca gc	282

<210> SEQ ID NO 171
<211> LENGTH: 282
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence

-continued

<220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV15*02

<400> SEQUENCE: 171

gatgccatgg tcataccagaa cccaaagatac caggtaacc	60
ctgagttgtt ctcaagacttt gaaccataac gtcatgtact	120
caggccccaa agctgctgtt ccactactat gacaaagatt	180
cctgataact tccaaatccag gaggccgaac acttcttct	240
ccaggcctgg gggacgcagc catgtacctg tgtgccacca	282

<210> SEQ ID NO 172
 <211> LENGTH: 290
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV16*01

<400> SEQUENCE: 172

ggtaagaag tcgcccagac tccaaaacat cttgtcagag	60
ttatatttgtc ccccaataaaa aggacacagt tatgtttttt	120
aacgagttca agttcttgat ttcccttcag aatgaaaatg	180
cccaaggaaa gattttcage taagtgcctc ccaaattcac	240
gtacgaagc ttgaggattc agcagtgtat ttttgtgcca	290

<210> SEQ ID NO 173
 <211> LENGTH: 290
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV16*02

<400> SEQUENCE: 173

ggtaagaag tcgcccagac tccaaaacat cttgtcagag	60
ttatatttgtc ccccaataaaa aggacacagt taggtttttt	120
aacgagttca agttcttgat ttcccttcag aatgaaaatg	180
cccaaggaaa gattttcage taagtgcctc ccaaattcac	240
gtacgaagc ttgaggattc agcagtgtat ttttgtgcca	290

<210> SEQ ID NO 174
 <211> LENGTH: 285
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV16*03

<400> SEQUENCE: 174

ggtaagaag tcgcccagac tccaaaacat cttgtcagag	60
--	----

-continued

ttagtattgtg ccccaataaaa aggacacagt tatgtttttt ggtaccaaca ggtcctgaaa	120
aacgaggtca agtttttgtt ttccttccag aatgaaaatg tctttatgtga aacaggatcg	180
cccaaggaaa gatttcagc taagtgcctc ccaaattcac cctgtacgttg tgagatccag	240
gctacgaagc ttgaggattc agcagtgtat ttttgtgcca gcagc	285

<210> SEQ ID NO 175
<211> LENGTH: 287
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV17*01

<400> SEQUENCE: 175

gaggcctggag tcagccagac ccccagacac aaggtcacca acatgggaca ggaggtgatt	60
ctgaggtgcg atccatcttc tggtcacatg tttgttcaact ggtaccgaca gaatctgagg	120
caagaaatga agttgtgtat ttccttccag taccaaaaca ttgcagttga ttcaaggatg	180
cccaaggaaac gattcacagc tgaaaagacct aacggAACgt ctccacgct gaagatccat	240
cccgccagagc cgaggactc agcgtgtat ctctacagta ggggtgg	287

<210> SEQ ID NO 176
<211> LENGTH: 290
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV18*01

<400> SEQUENCE: 176

aatgcccccg tcatgcagaa cccaagacac ctggtcagga ggaggggaca ggaggcaaga	60
ctgagatgca gccaatgaa aggacacagt catgtttact ggtatcgca gctccagag	120
gaaggctcgt aattcatgtt ttatctccag aaagaaaata tcatacatgt gtcaggaatg	180
ccaaaggaaac gatTTCTGc tgaatttccc aaagagggcc ccagcatctt gaggatccag	240
caggtagtgc gaggagattc ggcagcttat ttctgtgcca gtcaccacc	290

<210> SEQ ID NO 177
<211> LENGTH: 287
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV19*01

<400> SEQUENCE: 177

gatgggtggaa tcactcagtc cccaaagtac ctgttcagaa aggaaggaca gaatgtgacc	60
ctgagttgtg aacagaattt gaaccacatg gccatgtact ggtaccgaca ggaccagg	120
caagggtctga gattgtatcta ctactcacag atagtaatg actttcagaa aggatata	180
gctgaagggt acagcgtctc tcgggagaag aaggaatctt ttccctctcac tgtgacatcg	240
gcccaaaaga acccgacagc tttctatctc tgtgccagta gtataga	287

<210> SEQ ID NO 178

-continued

```

<211> LENGTH: 287
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV19*02

<400> SEQUENCE: 178

gatggggaa tcactcagtc cccaaagtac ctgttcagaa aggaaggaca gaatgtgacc      60
ctgagttgtg aacagaattt gaaccacgt gccatgtact ggtaccgaca ggtcccaggg      120
caaggggctga gattgatcta ctactcacac atagtaaatg actttcagaa aggagatata      180
gttgcagggt acagegtctc tcgggagaag aaggaatcct ttccctctcac tgtgacatcg      240
gccccaaaaga acccgacacgc tttctatctc tgtgccagta gtataga                  287

<210> SEQ ID NO 179
<211> LENGTH: 282
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV19*03

<400> SEQUENCE: 179

gatggggaa tcactcagtc cccaaagtac ctgttcagaa aggaaggaca gaatgtgacc      60
ctgagttgtg aacagaattt gaaccacgt gccatgtact ggtaccgaca ggaccgggg      120
caaggggctga gattgatcta ctactcacac atagtaaatg actttcagaa aggagatata      180
gttgcagggt acagegtctc tcgggagaag aaggaatcct ttccctctcac tgtgacatcg      240
gccccaaaaga acccgacacgc tttctatctc tgtgccagta gc                  282

<210> SEQ ID NO 180
<211> LENGTH: 291
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV20-1*05

<400> SEQUENCE: 180

ggtgctgtcg tctctcaaca tccgagcagg gttatctgta agagtggAAC ctctgtgaag      60
atcgagtgcc gttccctgga ctttcaggcc acaactatgt tttggtatcg tcagttccg      120
aaaaagagtc tcatgctgtatggcacttcc aatgaggggct ccaaggccac atacgagcaa      180
ggcgctcgaga aggacaagtt tctcatcaac catgcaagcc tgaccttgc cactctgaca      240
gtgaccaggtagt cccatcctga agacagcgc ttctacatct gcagtgtctag a          291

<210> SEQ ID NO 181
<211> LENGTH: 291
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV20-1*07

<400> SEQUENCE: 181

```

-continued

ggtgctgtcg tctctcaaca tccgagcagg gttatctgt a agagtggAAC ctctgtgaag	60
atcgagtGCC gttccCTGGA ctTTcAGGCC acaactatgt ttTggtatcg tcagttCCG	120
aaaaagagtc tcatgcAGAT cgcaACTTCC aatgaggGCt ccaaggccAC atacgagCAA	180
ggcgtcgaga aggacaAGTT tctcatcaac catgcaAGCC tgacCTTGTc cactctgaca	240
gtgaccagtG cccatCCTGA agacAGCAGC ttctacatct gcagtgtAG a	291

<210> SEQ ID NO 182
<211> LENGTH: 291
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV20-1*04

<400> SEQUENCE: 182	
ggtgctgtcg tctctcaaca tccgagcagg gttatctgt a agagtggAAC ctctgtgaag	60
atcgagtGCC gttccCTGGA ctTTcAGGCC acaactatgt ttTggtatcg tcagttCCG	120
aaaaagagtc tcatgctgat ggcaACTTCC aatgaggGCt ccaaggccAC atacgagCAA	180
ggcgtcgaga aggacaAGTT tctcatcaac catgcaAGCC tgacCTTGTc cactctgaca	240
gtgaccagtG cccatCCTGA agacAGCAGC ttctacatct gcagtgtAG t	291

<210> SEQ ID NO 183
<211> LENGTH: 288
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV20-1*06

<400> SEQUENCE: 183	
ggtgctgtcg tctctcaaca tccgaggTAGG gttatctgt a agagtggAAC ctctgtgaag	60
atcgagtGCC gttccCTGGA ctTTcAGGCC acaactatgt ttTggtatcg tcagttCCG	120
aaaaagagtc tcatgctgat ggcaACTTCC aatgaggGCt ccaaggccAC atacgagCAA	180
ggcgtcgaga aggacaAGTT tctcatcaac catgcaAGCC tgacCTTGTc cactctgaca	240
gtgaccagtG cccatCCTGA agacAGCAGC ttctacatct gcagtgtGCT	288

<210> SEQ ID NO 184
<211> LENGTH: 288
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV20-1*02

<400> SEQUENCE: 184	
ggtgctgtcg tctctcaaca tccgagcagg gttatctgt a agagtggAAC ctctgtgaag	60
atcgagtGCC gttccCTGGA ctTTcAGGCC acaactatgt ttTggtatcg tcagttCCG	120
aaacagagtc tcatgctgat ggcaACTTCC aatgaggGCt ccaaggccAC atacgagCAA	180
ggcgtcgaga aggacaAGTT tctcatcaac catgcaAGCC tgacCTTGTc cactctgaca	240
gtgaccagtG cccatCCTGA agacAGCAGC ttctacatct gcagtgtGCT	288

-continued

<210> SEQ_ID NO 185
<211> LENGTH: 293
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV20-1*01

<400> SEQUENCE: 185

ggtgctgtcg tctctcaaca tccgagctgg gttatctgtt agagtggAAC ctctgtgaag	60
atcgagtGCC gttccCTGGA ctttcAGGCC acaactatgt tttggtatcg tcagttCCCG	120
aaacagAGTC tcatgtGTAT ggcaacttcc aatgaggGGCT ccaaggccAC atacgagCAA	180
ggcgtcgaga aggacaagtt tctcatcaac catgcaagcc tgaccttGTC cactctgaca	240
gtgaccaggTG cccatcCTGA agacagcAGC ttctacatct gcagtgtAGA	293

<210> SEQ_ID NO 186
<211> LENGTH: 288
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV20-1*03

<400> SEQUENCE: 186

ggtgctgtcg tctctcaaca tccgagctgg gttatctgtt agagtggAAC ctctgtgaag	60
atcgagtGCC gttccCTGGA ctttcAGGCC acaactatgt tttggtatcg tcagttCCCG	120
aaacagAGTC tcatgtGTAT ggcaacttcc aatgaggGGCT gcaaggccAC atacgagCAA	180
ggcgtcgaga aggacaagtt tctcatcaac catgcaagcc tgaccttGTC cactctgaca	240
gtgaccaggTG cccatcCTGA agacagcAGC ttctacatct gcagtgtAGA	288

<210> SEQ_ID NO 187
<211> LENGTH: 290
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV21-1*01

<400> SEQUENCE: 187

gacaccaagg tcacccagAG acctagactt ctggtaAAAG caagtGAACA gaaAGCAAAG	60
atggattgtg ttccCTATAAA agcacatAGT tatgtttACT ggtatcgtaA gaagctggAA	120
gaagAGCTA agTTTTGGT ttactttcAG aatgaAGAAC ttattcAGAA agcAGAAATA	180
atcaatgAGC gatTTTAGC ccaatGCTCC aaaaACTCAT CCTGTACCTT ggAGATCCAG	240
tccacggAGT caggGGACAC agcactgtAT ttctgtGCCA gcagcaaAGC	290

<210> SEQ_ID NO 188
<211> LENGTH: 288
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:

-continued

<223> OTHER INFORMATION: TRBV22-1*01

<400> SEQUENCE: 188

gatgctgaca tctatcagat gccattccag ctcactgggg ctggatggga tgtgactctg	60
gagtggaaac ggaattttag acacaatgac atgtactgct actggactctg gcaggaccca	120
aagcaaaatc tgagactgat ctattactca agggttgaaa agatattca gagaggagat	180
ctaactgaag gtaactgttc tgccaagagg agaaggggc atttcttctc agggtaagt	240
tggcccacac cagccaaaca gctttgtact tctgtctgg gagcgac	288

<210> SEQ ID NO 189
<211> LENGTH: 290
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV23-1*01

<400> SEQUENCE: 189

catgccaaag tcacacagac tccaggacat ttggtaaaag gaaaaggaca gaaaacaaag	60
atggattgtt ccccccggaaaa aggacatact tttgttttat ggtatcaaca gaatcagaat	120
aaagagttt tgcttttgat ttcctttcag aatgaacaag ttcttcaaga aacggagatg	180
cacaagaagc gatttcatac tcaatgcccc aagaacgcac cctgcagcct ggcaatcctg	240
tcctcagaac cgggagacac ggcactgtat ctctgcgccca gcagtcaatc	290

<210> SEQ ID NO 190
<211> LENGTH: 288
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV24-1*01

<400> SEQUENCE: 190

gtatgtatgtt tacccagac cccaaaggaaat aggatcacaa agacaggaaa gaggattatg	60
ctggaaatgtt ctcagactaa gggcatgtat agaatgtact ggtatcgaca agacccagga	120
ctgggcctac ggttcatcta ttactcctt gatgtcaaag atataaacaaggagatc	180
tctgtatgtt acagtgtctc tcgacaggca caggctaaat tctccctgtc cctagatct	240
gcacatccccca accagacagc tctttacttc tggccacca gtgatttg	288

<210> SEQ ID NO 191
<211> LENGTH: 287
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV25-1*01

<400> SEQUENCE: 191

gaagctgaca tctaccagac cccaaagatac cttgtttag ggacaggaaa gaagatcact	60
ctggaaatgtt ctcacccat gggccatgc aaaatgtact ggtatcaaca agatccagga	120
atggaaactac acctcatcca ctattcctat ggagttaaat ccacagagaa gggagatctt	180

-continued

tccctctgagt caacagtctc cagaataagg acggagcatt ttcccctgac cctggagtct 240

gccaggccct cacatacctc tcagtagtac tgcgtccagca gtgaata 287

<210> SEQ ID NO 192

<211> LENGTH: 287

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<220> FEATURE:

<223> OTHER INFORMATION: TRBV26*01

<400> SEQUENCE: 192

gatgctgttag ttacacaatt cccaagacac agaatcattt ggacaggaaa ggaattcatt 60

ctacagtgtt occagaatat gaatcatgtt acaatgtact ggtatcgaca ggaccaggaa 120

cttggactga agctggctta ttattcacctt ggcactggaa gcactgaaaa aggagatatc 180

tctgaggggt atcatgtttc ttgaaataact atagcatttt ttcccctgac cctgaagtct 240

gccagcacca accagacatc tgcgttatctc tatgccagca gttcatc 287

<210> SEQ ID NO 193

<211> LENGTH: 287

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<220> FEATURE:

<223> OTHER INFORMATION: TRBV27*01

<400> SEQUENCE: 193

gaagccccaa tgacccagaa cccaagatac ctcatcacag tgactggaaa gaagtttaca 60

gtgacttgtt ctcagaatat gaaccatgat tatatgtctt ggtatcgaca agacccagg 120

ctggggcttaa ggcagatcta ctattcaatg aatgttgggg tgactgataa gggagatgtt 180

cctgaagggtt acaaaatctc tcgaaaagag aagagaaattt tccccctgat cctggagtcg 240

cccagccccca accagacatc tctgtacttc tgcgtccagca gtttatac 287

<210> SEQ ID NO 194

<211> LENGTH: 287

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<220> FEATURE:

<223> OTHER INFORMATION: TRBV28*01

<400> SEQUENCE: 194

gatgtgaaag taacccagag ctcgagatat ctatgtaaaa ggacgggaga gaaagtttt 60

cttggatgtt tccaggatat ggaccatgaa aatatgtctt ggtatcgaca agacccagg 120

ctggggctac ggctgtatcta ttatctatat gatgttaaaa tgaaagaaaa aggagatatt 180

cctgaggggtt acagtgtctc tagagagaag aaggagcgct totcccctgat tctggagtc 240

gccagcacca accagacatc tatgtacatc tgcgtccagca gtttatac 287

<210> SEQ ID NO 195

<211> LENGTH: 290

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

-continued

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<220> FEATURE:

<223> OTHER INFORMATION: TRBV29-1*01

<400> SEQUENCE: 195

agtgcgtca tctctaaaa gccaaggcagg gatatctgtc aacgtggAAC ctccctgacg	60
atccagtgTC aagtcgatAG ccaagtcacc atgatgttCT ggtaccGTCA gcaacctGGA	120
cagagcCTGA cactgtatCGC aactgcaAT cagggctCTG aggccacata tgagagtGGA	180
tttgtcATTG acaagTTCC catcagCCGC ccaaACCTAA cattctcaAC tctgactGTG	240
agcaacatGA gcccTGAAGA cagcagcATA tatctctGCA gcgttGAA	290

<210> SEQ ID NO 196

<211> LENGTH: 288

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<220> FEATURE:

<223> OTHER INFORMATION: TRBV29-1*02

<400> SEQUENCE: 196

agtgcgtca tctctaaaa gccaaggcagg gatatctgtc aacgtggAAC ctccctgacg	60
atccagtgTC aagtcgatAG ccaagtcacc atgatgttCT ggtaccGTCA gcaacctGGA	120
cagagcCTGA cactgtatCGC aactgcaAT cagggctCTG aggccacata tgagagtGGA	180
tttgtcATTG acaagTTCC catcagCCGC ccaaACCTAA cattctcaAG tctgactGTG	240
agcaacatGA gcccTGAAGA cagcagcATA tatctctGCA gcgttGAA	288

<210> SEQ ID NO 197

<211> LENGTH: 231

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<220> FEATURE:

<223> OTHER INFORMATION: TRBV29-1*03

<400> SEQUENCE: 197

acgatccagt gtcaagtGCA tagccaAGTC accatgataT tctggTaccG tcagcaacct	60
ggacagAGCC tgacactGAT cgcaactGCA aatcaggGCT ctgaggccAC atatgagAGT	120
ggatttGTCA ttgacaAGTT tccccatcAGC cgcccaaACC taacattCTC aactctGACT	180
gtgagcaACA tgagccCTGA agacAGCAGC atatatCTCT gcagcgcGGG C	231

<210> SEQ ID NO 198

<211> LENGTH: 284

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<220> FEATURE:

<223> OTHER INFORMATION: TRBV30*02

<400> SEQUENCE: 198

tctcagactA ttcatcaATG gccagcGACC ctggTgcAGC ctgtggGAG cccgtctCT	60
ctggagTGCA ctgtggAGGG aacatcaAAc cccaaCCTAT actggTaccG acaggcTGCA	120
ggcaggGGCC tccagcGTCT cttctactCC gttggTattG gccagatcAG ctctgaggTG	180

-continued

ccccagaatc tctcagcctc cagaccccaag gaccggcagt tcatacctgag ttctaagaag	240
ctccttctca gtgactctgg cttctatctc tgtgcctgga gtgt	284

<210> SEQ ID NO 199
<211> LENGTH: 282
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV30*05

<400> SEQUENCE: 199

ttcagacta ttcatcaatg gccagcgacc ctgggtgcagc ctgtggcag cccgctctcc	60
ctggagtgca ctgtggaggg aacatcaaac cccaacctat actggtaccg acaggctgca	120
ggacggggcc tccagctgct cttctactcc gttggatttg gccagatcag ctctgaggtg	180
ccccagaatc ttcagcctc cagaccccaag gaccggcagt tcatacctgag ttctaagaag	240
ctccttctca gtgactctgg cttctatctc tgtgcctgga ga	282

<210> SEQ ID NO 200
<211> LENGTH: 284
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV30*01

<400> SEQUENCE: 200

ttcagacta ttcatcaatg gccagcgacc ctgggtgcagc ctgtggcag cccgctctct	60
ctggagtgca ctgtggaggg aacatcaaac cccaacctat actggtaccg acaggctgca	120
ggcaggggcc tccagctgct cttctactcc gttggatttg gccagatcag ctctgaggtg	180
ccccagaatc ttcagcctc cagaccccaag gaccggcagt tcatacctgag ttctaagaag	240
ctccttctca gtgactctgg cttctatctc tgtgcctgga gtgt	284

<210> SEQ ID NO 201
<211> LENGTH: 276
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TRBV30*04

<400> SEQUENCE: 201

actatttcattc aatggccagc gaccctggtg cagcctgtgg gcagcccgct ctctctggag	60
tgcactgtgg agggAACATC aaACCCCAAC ctatactggt accgacaggc tgcaggcagg	120
ggcctccagc tgctttctca cttccattggt attgaccaga tcagctctga ggtgcggccag	180
aatctctcag cttccagacc ccaggacgg cagttcattc tgagttctaa gaagctcctc	240
ctcagtgact ctggcttctta tctctgtgcc tggagt	276

<210> SEQ ID NO 202
<211> LENGTH: 448
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence

-continued

<220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TCRBJ1S1

<400> SEQUENCE: 202

ttgaaaaagg aacctaggac cctgtggatg gactctgtca ttctccatgg tcctaaaaag	60
caaaagtcaa agtgttcttc tgtgtatac ccataaagca caggaggaga tttcttagct	120
cactgtcctc catccttagcc agggccctct cccctctcta tgccttcaat gtgatttca	180
ccttgacccc tgtcactgtg tgaacactga agtttctt ggacaaggca ccagactcac	240
agttgttaggt aagacatttt tcaggttctt ttgcagatcc gtcacaggga aaagtgggtc	300
cacagtgtcc cttttagagt ggctatattc ttatgtgcta actatggcta cacctcggt	360
tccggggacca ggtaaccgt tgttaggtaag gctgggggtc tctaggaggg gtgcgtatgag	420
ggaggactct gtcctggaa atgtcaaa	448

<210> SEQ ID NO 203
 <211> LENGTH: 448
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TCRBJ1S2

<400> SEQUENCE: 203

gccagggccc tctccctct ctagccttc aatgtgattt tcaccttgac ccctgtcact	60
gtgtgaacac tgaagcttcc tttggacaag gcaccagact cacagttgtt ggttaagacat	120
tttcaggtt ctttgcaga tccgtcacag ggaaaagtgg gtccacagtg tcccttttag	180
agtggctata ttcttatgtg ctaactatgg ctacacccctt ggttcgggca ccaggtaac	240
cgttgttaggt aaggctgggg gtcctcttagga ggggtgcgtt gagggaggac tctgtcctgg	300
gaaatgtcaa agagaacacaga gatcccaatcccgagcca gactgaggga gacgtcatgt	360
catgtccccgg gattgagttc aggggaggctt ccctgtgagg gcaaatccac ccaggctcc	420
cagaggctct gaggcgtcac agctgagc	448

<210> SEQ ID NO 204
 <211> LENGTH: 450
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TCRBJ1S3

<400> SEQUENCE: 204

gattttatag gaggccactc tgggtcttctt tttgtcacct gcctgagttc tgggcaagct	60
cttggaaaggaa acacagagta ctggaaagcag agctgctgtc cctgtgaggg aagagttccc	120
atgaactcccccc aacctctgcc tgaatccccag ctgtgctcag cagagactgg ggggttttga	180
agtggccctg ggaggctgtg ctctggaaac accatatattt ttggagaggg aagttggctc	240
actgtgttagt gtgagtagt caaggctggaa cagctgggaa ctggcaaaaa ggggttggaa	300
tccagacgga gcctttgtct ctagtgctta ggtgaaagtg tatttttgc aggaaggct	360
atgaggcaga tgaggaggaa atagccccc tctcctctcg actatttgt agactgctg	420

-continued

tgc caaggta ggttccctta ctgagagatg	450
-----------------------------------	-----

<210> SEQ ID NO 205
<211> LENGTH: 451
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TCRBJ1S4

<400> SEQUENCE: 205

cagaagaggg aacttggggg atcacacggg gcctaattgg tctgctgacc accgcattt	60
gggttgtacc attgtctacc cctctacca ccagggttaa aattctacta aggaacagga	120
gaggacctgg caggtggact tggggaggca ggagtggaaag gcagcaggc gcggtttcc	180
ttccagtc ttatgttgtg caactaatga aaaactgttt ttggcagtg gaaccagct	240
ctctgttgc gtatgtaaa agacttctt cgggatgtg tatcataagg tcggagtcc	300
aggaggaccc cttgcgggag ggcagaaact gagaacacag ccaagaaaag ctcataaaat	360
gtgggtcagt ggagtgtgtg gtggggcccc aagagttctg tgtgtaaagca gcttctggaa	420
ggaaggggccc acaccagctc ctctggggtt t	451

<210> SEQ ID NO 206
<211> LENGTH: 450
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TCRBJ1S5

<400> SEQUENCE: 206

gatagtgtat cataaggtcg gagttccagg aggaccctt gcgggaggc agaaactgag	60
aacacagcca agaaaagctc ataaaatgtg ggtcagtgg gtgtgtggg gggcccaag	120
agttctgtgt gtaagcagct tctggaaagga agggcccaca ccagctcc tcgggtttgc	180
cacactcatg atgcactgtg tagcaatcg cccagcat tttgtatgg gactcgactc	240
tccatcttag gtaagttgca gaatcagggt ggtatggca ttgtcccttg aaggcagagt	300
tctctgttcc tcctcccggt gctggtgagg cagattgagt aaaatctt accccatggg	360
gtaagagctg tgccctgtgcc tgccgttccct ttgggtgtgtc ttgggtgact cctctatssc	420
tcttctctaa gtcttcagtc cataatctgc	450

<210> SEQ ID NO 207
<211> LENGTH: 453
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TCRBJ1S6

<400> SEQUENCE: 207

atggctctgc ctctcttaag ccttttcttc ttgcgcctta tgctgcacag tatgtttagg	60
cctttttcct aacagaatcc ctttggtcca gagccatgaa tccaggcaga gaaaggcagc	120
catcctgtctg tcagggagct aagacttgcc ctctgactgg agatcgccgg gtgggttta	180

-continued

tctaaggctc tgcagctgtg ctcctataat tcacccctcc actttggaa cgggaccagg	240
ctcaactgtga caggatggg ggctccactc ttgactcggg ggtgcctggg tttgaactgca	300
atgatcagtt gctggaaagg gaattgagtg taagaacgga ggtcagggtc accccttctt	360
acctggagca ctgtgccctc tcctccctc cctggagtc ttccagcttg ttgcctgtct	420
gtgttgccctg cagttcctca gctgttagac tcc	453

<210> SEQ ID NO 208
<211> LENGTH: 449
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TCRBJ2S1

<400> SEQUENCE: 208	
aatccactgt gttgtccccc agccaagtgg attctcctct gcaaatttgt ggtggcctca	60
tgcaagatcc agttaccgtg tccagctaac tcgagacagg aaaagatagg ctcaggaaag	120
agaggaaggg tgcgcctct gtctgtgcta agggaggtgg ggaaggagaa ggaattctgg	180
gcagccccctt cccactgtgc tcctacaatg agcagttctt cgggcccagg acacggctca	240
ccgtgctagg taagaagggg gctccaggtg ggagagagg tgagcagccc agcctgcacg	300
accccagaac cctgttctta ggggagtgaa cactgggcaa tccaggccc tcctcgaggg	360
aagcggggtt tgcgccaggg tccccagggc tgtgcgaaca ccggggagct gtttttggaa	420
gaaggctcta ggctgaccgt actgggtaa	449

<210> SEQ ID NO 209
<211> LENGTH: 451
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TCRBJ2S2

<400> SEQUENCE: 209	
ctgtgtcct acaatgagca gtttttcggg ccagggacac ggctcaccgt gctaggtaa	60
aagggggctc caggtggag agagggttag cagcccgaccc cagaaccctg	120
ttcttagggg agtggacact gggcaatcca gggccctct cgagggaaagc ggggttgcg	180
ccagggtccc caggctgtg cgaacaccgg ggagctgttt ttggagaag gctctagct	240
gaccgtactg ggttaaggagg cggttgggc tccggagac tccgagagg cggatggc	300
agaggttaagc agctgccccca ctctgagagg ggctgtgctg agagggcgtg ctggcgct	360
gggcggagga ctccctgggttc tgggtgctgg gagagcgatg gggctctcag cgggtggaaag	420
gaccggagct gagtctggaa cagcagagcg g	451

<210> SEQ ID NO 210
<211> LENGTH: 449
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TCRBJ2S3

-continued

<400> SEQUENCE: 210

gggcgggatg	ggcagaggta	agcacgtgcc	ccactctgag	aggggctgtg	ctgagaggcg	60
ctgctggcg	tctggcgga	ggactcctgg	ttctgggtgc	tgggagagcg	atggggctct	120
cagcggtggg	aaggacccga	gctgagtcg	ggacagcaga	gccccggcaga	ccggtttttg	180
tcttggcc	ccaggctgtg	agcacagata	cgcagtattt	tggcccaggc	accggctga	240
cagtgtcg	taageggggg	ctcccgctga	agcccccggaa	ctggggaggg	ggcgecccg	300
gacgcggggg	gcgtcgagg	gccagtttct	gtgccgcgtc	tggggctgt	gagccaaaaa	360
cattcagtag	ttcggcgccg	ggacccggct	ctcaagtgtc	ggtaagctgg	ggccgcggg	420
ggaccggggg	cgagactgcg	ctcgggttt				449

<210> SEQ ID NO 211

<211> LENGTH: 450

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
polynucleotide

<220> FEATURE:

<223> OTHER INFORMATION: TCRBJ2S4

<400> SEQUENCE: 211

gacagcagag	cgggcagcac	cggttttgt	cctgggcctc	caggctgtga	gcacagatac	60
cgagtatttt	ggcccaggca	cccggtgac	agtgtcggt	aagcggggc	tcccgtgaa	120
gccccggaa	tcggggagggg	gccccgggg	acgccccggg	cgtcgagg	ccagttctg	180
tgcgcgtct	cggggctgtg	agccaaaaac	attcagta	tccggccgg	gaccggctc	240
tcaagtgtgg	gtaaagctggg	gccgcgggg	gaccggggac	gagactgcgc	tccggtttt	300
gtgcggggct	cggggccgt	gaccaagaga	cccaagtactt	ccggccaggc	acgcggctcc	360
tggtgctcgg	tgagcgcggg	ctgctggggc	gccccggcgg	ccggcttggg	tctggtttt	420
ccggggagtc	cccggtgt	gtctggggc				450

<210> SEQ ID NO 212

<211> LENGTH: 448

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
polynucleotide

<220> FEATURE:

<223> OTHER INFORMATION: TCRBJ2S5

<400> SEQUENCE: 212

ccccggaa	ggggaggggg	cggccggggc	gtcgcaaggc	cagttctgt		60
gccgcgtctc	ggggctgtga	gcca	ttcagta	ccggccgggg	accggctct	120
cagtgtggg	taagctgggg	ccggccgggg	acggggacg	agactgcgt	ccggtttttg	180
tgcggggctc	ggggccgtg	accaagagac	ccagta	ggccaggc	cgccgtct	240
ggtgtcggt	gagcgcggg	tgctggggcg	ccggcgcggg	ccggcttggg	tctggtttg	300
ccggggatcc	ccgggtgt	ctctggggcc	aacgtctga	cttgcgggc	ccgcagg	360
ctgaccgtgc	tgggtgagtt	ttcgcggac	cacccggggcg	ccgggattca	ggtggaaaggc	420
ggccggctgt	tgcggcacc	cggtccgg				448

<210> SEQ ID NO 213

-continued

```

<211> LENGTH: 453
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TCRBJ2S6

<400> SEQUENCE: 213

cagtgtggg taagctgggg ccgcgcgggg accggggacg agactgcgt cgggttttg      60
tgcggggctc gggggccgtg accaaagagac ccagtacttc gggccaggca cgccggctct    120
ggtgtcggtt gagcgcgggc tgctggggcg cggccgggg cggcttgggt ctgggttttg    180
cgggggatcc cccggctgtg ctctggggcc aacgtcctga ctttcggggc cggcagcagg    240
ctgaccgtgc tgggtgagtt ttgcgggac caccggggc gggggattca ggtggaaaggc    300
ggcggtgtct tcgcggcacc cggtccggcc ctgtgctggg agacctgggc tgggtcccc    360
gggtggggcag gagctgggg agccttagag gtttgcatgc ggggggtgcac ctccgtgctc    420
ctacgagcag tacttcgggc cgggcaccag gct                                453

```

```

<210> SEQ ID NO 214
<211> LENGTH: 447
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: TCRBJ2S7

<400> SEQUENCE: 214

tgactttcgg ggccggcagc aggctgaccg tgctgggtga gttttcgccc gaccaccgg      60
gcggcgggat tcaggtggaa ggccggggct gcttcggcc acccggtccg gccctgtgt    120
gggagacactg ggctgggtcc ccagggtggg caggagctcg gggagcccta gaggttgca    180
tgccccgggtg caccctccgtg ctccctacgag cagtaatccg ggccgggcac caggctcacg    240
gtcacaggtg agattcgggc gtctccccac ctccctacgag cttccatggcc ctccgtcccc    300
ggtggaccgg agctggagga gctgggtgtc cgggggtcagc tctgcaaggt cacctcccc    360
ctccctggggaa aagactgggg aagaggggagg ggggtggggag gttgtcagag tccggaaagc    420
tgagcagagg gcgaggccac ttttaat                                447

```

```

<210> SEQ ID NO 215
<211> LENGTH: 50
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 215

gaattattat aagaaaactct ttggcagtgg aacaacactg gttgtcacag                                50

```

```

<210> SEQ ID NO 216
<211> LENGTH: 50
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 216

gaattattat aagaaaactct ttggcagtgg aacaacactt gttgtcacag                                50

```

```

<210> SEQ ID NO 217
<211> LENGTH: 47

```

-continued

<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 217

```
ttattataag aaactcttg gcagtggAAC aacacttggT gtcacAG 47
```

<210> SEQ ID NO 218
<211> LENGTH: 60
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 218

```
tgggcaAGAG ttggcaAAA aatcaaggT atttggTccc ggaacaAAGC ttatcattAC 60
```

<210> SEQ ID NO 219
<211> LENGTH: 60
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 219

```
ataccactgg ttggTTcaag atatTTgCTG aaggGactaa gctcatAGTA actTCACCTG 60
```

<210> SEQ ID NO 220
<211> LENGTH: 60
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 220

```
atagtATGta ttggatcaag acgtttgcaa aaggGactaG gctcatAGTA actTCGcCTG 60
```

<210> SEQ ID NO 221
<211> LENGTH: 300
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 221

```
tcttccaACT ttggaaGGGAAG aacgaAGTCA gtcatcAGGC agactGGGTc atctgCTGAA 60
atcacttGTG atcttGCTGA aggaAGTAAc ggctacatCC actggTACCT acaccAGGAG 120
ggaaAGGCC CACAGCGTCT tcagtactat gactcctACA actCCAAGGT tGTGTTGGAA 180
tcaggAGTCA gtccAGGGAA gtattataCT tacgcaAGCA caagGAACAA cttGAGATTG 240
atactgcAA AtctaattGA aaatgACTCT gggGTCTATT actgtGCCAC ctggGACGGG 300
```

<210> SEQ ID NO 222
<211> LENGTH: 297
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 222

```
tcttccaACT ttggaaGGGAAG aacgaAGTCA gtcatcAGGC agactGGGTc atctgCTGAA 60
atcacttGTG atcttGCTGA aggaAGTAAc ggctacatCC actggTACCT acaccAGGAG 120
ggaaAGGCC CACAGCGTCT tcagtactat gactcctACA actCCAAGGT tGTGTTGGAA 180
tcaggAGTCA gtccAGGGAA gtattataCT tacgcaAGCA caagGAACAA cttGAGATTG 240
atactgcAA AtctaattGA aaatgACTCT gggGTCTATT actgtGCCAC ctggGACGGG 297
```

<210> SEQ ID NO 223
<211> LENGTH: 300
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 223

tcttccaact	tggaaggggag	aacgaagtca	gtcatcagggc	agactgggtc	atctgctgaa	60
atcacttgtg	atcttgcgt	agaaggtaacc	ggctacatcc	actggtaacct	acaccaggag	120
gggaaggccc	cacagcgctc	tctgtactat	gactcctaca	cctccagcgt	tgtgttgaa	180
tcaggaatca	gccccaggaa	gtatgatact	tatggaagca	caaggaagaa	cttgagaatg	240
atactgcgaa	atcttattga	aatgactct	ggagtctatt	actgtgccac	ctgggatggg	300

<210> SEQ ID NO 224

<211> LENGTH: 300
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 224

tcttccaact	tggaaggggag	aacgaagtca	gtcatcagggc	agactgggtc	atctgctgaa	60
atcacttgtg	atcttgcgt	agaaggtaacc	ggctacatcc	actggtaacct	acaccaggag	120
gggaaggccc	cacagcgctc	tctgtactat	gactcctaca	cctccagcgt	tgtgttgaa	180
tcaggaatca	gccccaggaa	gtatgatact	tacggaagca	caaggaagaa	cttgagaatg	240
atactgcgaa	atcttattga	aatgactct	ggagtctatt	actgtgccac	ctgggatggg	300

<210> SEQ ID NO 225

<211> LENGTH: 300
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 225

tcttccaact	tggaaggggag	aacaaagtca	gtcaccaggc	caactgggtc	atcagctgta	60
atcacttgtg	atcttctgt	agaaaatgcc	gtctacaccc	actggtaacct	acaccaggag	120
gggaaggccc	cacagcgctc	tctgtactat	gactcctaca	actccagggt	tgtgttgaa	180
tcaggaatca	gtcgagaaaa	gtatcatact	tatgcaagca	cagggaaagag	ccttaaattt	240
atactggaaa	atctaattga	acgtgactct	gggtctatt	actgtgccac	ctgggatagg	300

<210> SEQ ID NO 226

<211> LENGTH: 297
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 226

tcttccaact	tggaaggggag	aacgaagtca	gtcaccaggc	tgactgggtc	atctgctgaa	60
atcacctgtg	atcttctgg	agcaaggtaacc	ttatacatcc	actggtaacct	gcaccaggag	120
gggaaggccc	cacagtgtc	tctgtactat	gaaccctact	actccagggt	tgtgttgaa	180
tcaggaatca	ctcccgaaaa	gtatgacact	ggaagcacaa	ggagcaattg	gaatttgaga	240
ctgcaaaatc	taattaaaaa	tgattctggg	ttctattact	gtgccacctg	ggacagg	297

<210> SEQ ID NO 227

<211> LENGTH: 300
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 227

tcttccaact	tggaaggggag	aacgaagtca	gtcaccaggc	agactgggtc	atctgctgaa	60
atcacttgcg	atcttactgt	aacaaatacc	ttctacatcc	actggtaacct	acaccaggag	120
gggaaggccc	cacagcgctc	tctgtactat	gacgtctcca	cggcaaggga	tgtgttgaa	180

-continued

tcaggactca gtccaggaaa gtattatact catacaccca ggaggtggag ctggatattg	240
agactgcaaa atctaattga aaatgattct ggggtctatt actgtgccac ctggacagg	300

<210> SEQ ID NO 228
<211> LENGTH: 299
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 228

ttttccaact tggaaggggag aacgaagtca gtcaccaggc agactgggtc atctgctgaa	60
atcaacttgcg atcttactgt aacaatacc ttctacatcc actggcacct acaccaggag	120
gggaaggccc cacagcgctc tctgtactat gacgtctcca ctgcaaggga tgtgttgaa	180
tcaggactca gtccaggaaa gtattatact catacaccca ggaggtggag ctggatattg	240
agactgcaaa atctaattga aaatgattct ggggtctatt actgtgccac ctggacag	299

<210> SEQ ID NO 229
<211> LENGTH: 300
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 229

ttttccaact tggaaggggag aatgaagtca gtcaccaggc cgactgggtc atctgctgaa	60
atcaacttgcg accttactgt aataaatgcc gtctacatcc actggcacct acageaggag	120
gggaagaccc cacagcatct tctgcactat gaagtctcca actcaaggga tgtgttgaa	180
tcaggctca gtcttgaaa gtattatact catacaccca ggaggtggag ctggatattg	240
agactgcaaa atctaattga aaatgattct ggggtctatt actgtgccac ctggggcagg	300

<210> SEQ ID NO 230
<211> LENGTH: 300
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 230

ttttccaact tggaaggggag aatgaagtca gtcaccaggc cgactgggtc atctgctgaa	60
atcaacttgcg accttactgt aataaatgcc gtctacatcc actggcacct acageaggag	120
gggaagaccc cacagcatct tctgcactat gatgtctcca actcaaggga tgtgttgaa	180
tcaggctca gtcttgaaa gtattatact catacaccca ggaggtggag ctggatattg	240
agactgcaaa atctaattga aaatgattct ggggtctatt actgtgccac ctggggcagg	300

<210> SEQ ID NO 231
<211> LENGTH: 300
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 231

ttttccaact tggaagggggg aacgaagtca gtcacgaggc cgacttaggtc atctgctgaa	60
atcaacttgcg accttactgt aataaatgcc ttctacatcc actggcacct acaccaggag	120
gggaaggccc cacagcgctc tctgtactat gacgtctcca actcaaaggaa tgtgttgaa	180
tcaggactca gtccaggaaa gtattatact catacaccca ggaggtggag ctggatattg	240
atactacgaa atctaattga aaatgattct ggggtctatt actgtgccac ctggacagg	300

<210> SEQ ID NO 232

-continued

```

<211> LENGTH: 311
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 232

ttatcaaagg tggagcagtt ccagctatcc atttccacgg aagtcaagaa aagtattgac      60
ataccttgca agatatcgag cacaagggtt gaaacagatg tcattcactg gtaccggcag     120
aaaccaaatac aggcttggga gcacctgatc tatattgtct caacaaaatc cgtagctcga     180
cgtagcatgg gtaagacaag caacaaagtg gaggcaagaa agaattctca aactctcact     240
tcaatcctta ccatcaagtc cgttagagaaa gaagacatgg ccgtttacta ctgtgctgctg     300
tgggggtgg c                                         311

<210> SEQ_ID NO 233
<211> LENGTH: 308
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 233

ttatcaaagg tggagcagtt ccagctatcc atttccacgg aagtcaagaa aagtattgac      60
ataccttgca agatatcgag cacaagggtt gaaacagatg tcattcactg gtaccggcag     120
aaaccaaatac aggcttggga gcacctgatc tatattgtct caacaaaatc cgtagctcga     180
cgtagcatgg gtaagacaag caacaaagtg gaggcaagaa agaattctca aactctcact     240
tcaatcctta ccatcaagtc cgttagagaaa gaagacatgg ccgtttacta ctgtgctgctg     300
tgggatta                                         308

<210> SEQ_ID NO 234
<211> LENGTH: 309
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 234

cttgggcagt tggaacaacc taaaatatct atttccagac cagcaaataa gagtgccac      60
atatcttggaa aggcatccat ccaaggcttt agcagtaaaa tcatacactg gtactggcag     120
aaaccaaaca aaggcttaga atatttatta catgtttct tgacaatctc tgctcaagat     180
tgctcaggtg ggaagactaa gaaacttgag gtaagtaaaa atgctcacac ttccacttcc     240
actttgaaaa taaagttctt agagaaagaa gatgaggtgg tgtaccactg tgccctgctgg     300
ataggcac                                         309

<210> SEQ_ID NO 235
<211> LENGTH: 309
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 235

cttgggcagt tggaacaacc taaaatatct atttccagac cagcaaataa gagtgccac      60
atatcttggaa aggcatccat ccaaggcttt agcagtaaaa tcatacactg gtactggcag     120
aaaccaaaca aaggcttaga atatttatta catgtttct tgacaatctc tgctcaagat     180
tgctcaggtg ggaagactaa gaaacttgag ataagtaaaa atgctcacac ttccacttcc     240
actttgaaaa taaagttctt agagaaagaa gatgaggtgg tgtaccactg tgccctgctgg     300
ataggcac                                         309

```

-continued

<210> SEQ ID NO 236
<211> LENGTH: 306
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 236

gcaggtcacc tagagcaacc tcaaattcc agtactaaaa cgctgtcaaa aacagccgc 60
ctggaatgtg tgggtgtctgg aataacaatt tctgcaacat ctgtatattg gtatcgagag 120
agacctggtg aagtcataca gttcctggtg tccatttcat atgacggcac tgtcagaaag 180
gaatctggca ttccgtcagg caaattttag gtggatagga tacctgaaac gtctacatcc 240
actctcacca ttcacaatgt agagaaacag gacatagcta cctactactg tgccttgtgg 300
gaggtg 306

<210> SEQ ID NO 237
<211> LENGTH: 306
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 237

gcaggtcacc tagagcaacc tcaaattcc agtactaaaa cgctgtcaaa aacagccgc 60
ctggaatgtg tgggtgtctgg aataaaaatt tctgcaacat ctgtatattg gtatcgagag 120
agacctggtg aagtcataca gttcctggtg tccatttcat atgacggcac tgtcagaaag 180
gaatctggca ttccgtcagg caaattttag gtggatagga tacctgaaac gtctacatcc 240
actctcacca ttcacaatgt agagaaacag gacatagcta cctactactg tgccttgtgg 300
gaggtg 306

<210> SEQ ID NO 238
<211> LENGTH: 285
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 238

ctcatcaggc cggagcagct ggccatgtc ctggggcaact agggaaagctt ggtcatcctg 60
cagtgcgtgg tccgcaccag gatcagctac acccactggt accagcagaa gggccaggc 120
cctgaggcac tccaccagct ggccatgtcc aagttggat tgcaagtggta ttccatcctg 180
aaagcagata aaatcatagc caaggatggc agcagctcta tcttggcagt actgaagttg 240
gagacaggca tcgagggcat gaactactgc acaacctggg ccctg 285

<210> SEQ ID NO 239
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 239

actactttga ctactggggc caaggaaccc tggtcaccgt ctctcttag 48

<210> SEQ ID NO 240
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 240

gctactttga ctactggggc caagggaccc tggtcaccgt ctctcttag 48

<210> SEQ ID NO 241

-continued

```

<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 241
actactttga ctactggggc cagggAACCC tggtcaccgt ctcctcag                                48

<210> SEQ ID NO 242
<211> LENGTH: 50
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 242
tgcatgtttt gatgtctggg gccaaggAACCC aatggtcacc gtctcttcag                                50

<210> SEQ ID NO 243
<211> LENGTH: 50
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 243
tgcatgtttt gatatctggg gccaaggAACCC aatggtcacc gtctcttcag                                50

<210> SEQ ID NO 244
<211> LENGTH: 63
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 244
attactacta ctactacggt atggacgtct gggggcaagg gaccacggtc accgtctcct                                60
cag                                63

<210> SEQ ID NO 245
<211> LENGTH: 62
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 245
attactacta ctactacggt atggacgtct gggggcaagg gaccacggtc accgtctcct                                60
ca                                62

<210> SEQ ID NO 246
<211> LENGTH: 63
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 246
attactacta ctactacggt atggacgtct gggggcaagg gaccacggtc accgtctcct                                60
cag                                63

<210> SEQ ID NO 247
<211> LENGTH: 62
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 247
attactacta ctactactac atggacgtct gggggcaagg gaccacggtc accgtctcct                                60
ca                                62

<210> SEQ ID NO 248
<211> LENGTH: 53

```

-continued

<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 248

```
ctactggtag ttcgatctct gggccgtgg caccctggtc actgtctcct cag
```

53

<210> SEQ ID NO 249
<211> LENGTH: 51
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 249

```
acaactggtt cgactcctgg ggccaaggaa ccctggtac cgtctctca g
```

51

<210> SEQ ID NO 250
<211> LENGTH: 51
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 250

```
acaactggtt cgaccctgg ggccagggaa ccctggtac cgtctctca g
```

51

<210> SEQ ID NO 251
<211> LENGTH: 52
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 251

```
gctgaatact tccagcactg gggccagggc accctggta ccgtctctc ag
```

52

<210> SEQ ID NO 252
<211> LENGTH: 61
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 252

```
gctacaagtg ctggagcac tggggcaggg cagccggac accgtctccc tggaaacgtc
```

60

a

61

<210> SEQ ID NO 253
<211> LENGTH: 54
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 253

```
aaagggtgctg ggggtccccct gaaccgcacc cgcctgaga ccgcagccac atca
```

54

<210> SEQ ID NO 254
<211> LENGTH: 52
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 254

```
cttgcggttg gacttccag ccgacagtgg tggtctggct tctgaggggt ca
```

52

<210> SEQ ID NO 255
<211> LENGTH: 296
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 255

```
cagggtcagc tggtgcaagtc tggagctgag gtgaagaagc ctggggcctc agtgaaggc
```

60

-continued

tccctgcagg cttctgggta caccttacc agctatggta tcagctgggt gcgacaggcc	120
cctggacaag ggcttgagtg gatgggatgg atcagcgctt acaaacttat	180
gcacagaagc tccagggcag agtcaccatg accacagaca catccacgag cacagctac	240
atggagctga ggagcctgag atctgacgac acggccgtgt attactgtgc gagaga	296

<210> SEQ ID NO 256

<211> LENGTH: 276

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 256

cagggtcagc tgggtcagtc tggagctgag gtgaagaagc ctggggcctc agtgaaggc	60
tccctgcagg cttctgggta caccttacc agctatggta tcagctgggt gcgacaggcc	120
cctggacaag ggcttgagtg gatgggatgg atcagcgctt acaaacttat	180
gcacagaagc tccagggcag agtcaccatg accacagaca catccacgag cacagctac	240
atggagctga ggagcctaaag atctgacgac acggcc	276

<210> SEQ ID NO 257

<211> LENGTH: 296

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 257

cagggtcagc tgggtcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggc	60
tccctgcagg cttctggata caccttacc ggctactata tgcactgggt gcgacaggcc	120
cctggacaag ggcttgagtg gatgggacgg atcaacccta acagtggttg cacaactat	180
gcacagaagt ttcagggcag ggtcaccatg accagggaca cgtccatcag cacagctac	240
atggagctga gcaggctgag atctgacgac acggcgtgt attactgtgc gagaga	296

<210> SEQ ID NO 258

<211> LENGTH: 296

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 258

cagggtcagc tgggtcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggc	60
tccctgcagg cttctggata caccttacc ggctactata tgcactgggt gcgacaggcc	120
cctggacaag ggcttgagtg gatgggatgg atcaacccta acagtggttg cacaactat	180
gcacagaagt ttcagggcag ggtcaccatg accagggaca cgtccatcag cacagctac	240
atggagctga gcaggctgag atctgacgac acggccgtgt attactgtgc gagaga	296

<210> SEQ ID NO 259

<211> LENGTH: 296

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<220> FEATURE:

<221> NAME/KEY: modified_base

<222> LOCATION: (113)..(113)

<223> OTHER INFORMATION: a, c, t or g

<400> SEQUENCE: 259

cagggtcagc tgggtcagtc tggggctgag gtgaagaagc ttggggcctc agtgaaggc	60
tccctgcagg cttctggata caccttacc ggctactata tgcactgggt gcnacaggcc	120
cctggacaag ggcttgagtg gatgggatgg atcaacccta acagtggttg cacaactat	180

-continued

gcacagaagt ttcagggcag ggtcaccatg accagggaca cgtccatcatc cacagcctac 240
 atggagctga gcaggctgag atctgacgac acggccgtgt attactgtgc gagaga 296

<210> SEQ ID NO 260
 <211> LENGTH: 294
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 260
 caggtgcagc tgggtgcagtc tggttgcagtc gtgaagaagc ctggggcctc agtgaaggc 60
 tcctgcaagg cttctggata caccttcacc ggctactata tgcactgggt gcgacaggcc 120
 cctggacaag ggcttgagtg gatgggatgg atcaacccta acagtggtgg cacaaactat 180
 gcacagaagt ttcagggctg ggtcaccatg accagggaca cgtccatcatc cacagcctac 240
 atggagctga gcaggctgag atctgacgac acggccgtgt attactgtgc gaga 294

<210> SEQ ID NO 261
 <211> LENGTH: 296
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 261
 caggttcagc tggtaacagtc tggttgcagtc gtgaagaagc ctggggcctc agtgaaggc 60
 tcctgcaagg ttccggata caccttcact gaattatcca tgcactgggt gcgacaggct 120
 cctggaaaag ggcttgagtg gatgggatgg ttgtatctg aagatggtaa aacaatctac 180
 gcacagaagt tccagggcag agtccaccatg accggggaca catctacaga cacagcctac 240
 atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc aacaga 296

<210> SEQ ID NO 262
 <211> LENGTH: 296
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 262
 caggttcagc ttgtgcagtc tggttgcagtc gtgaagaagc ctggggcctc agtgaaggtt 60
 tcctgcaagg cttctggata caccttcact agtcatgtca tgcattgggt gcgccaggcc 120
 cccggacaaa ggcttgagtg gatgggatgg atcaacgctg gcaatggtaa cacaaatat 180
 tcacagaagt tccagggcag agtccaccatt accggggaca catccgcgag cacagcctac 240
 atggagctga gcagcctgag atctgaagac acggctgtgt attactgtgc gagaga 296

<210> SEQ ID NO 263
 <211> LENGTH: 296
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 263
 caggttcagc ttgtgcagtc tggttgcagtc gtgaagaagc ctggggcctc agtgaaggtt 60
 tcctgcaagg cttctggata caccttcact agtcatgtca tgcattgggt gcgccaggcc 120
 cccggacaaa ggcttgagtg gatgggatgg agcaacgctg gcaatggtaa cacaaatat 180
 tcacaggagt tccagggcag agtccaccatt accggggaca catccgcgag cacagcctac 240
 atggagctga gcagcctgag atctgaggac atggctgtgt attactgtgc gagaga 296

<210> SEQ ID NO 264

-continued

```

<211> LENGTH: 296
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (295)..(295)
<223> OTHER INFORMATION: a, c, t or g

<400> SEQUENCE: 264
cagatgcagc tgggtcagtc tggggctgag gtgaagaaga ctgggtcc tc agtgaagg tt 60
tcctgc aagg cttccggata caccc tc acc taccgctacc tgcactgggt gcgacagg cc 120
ccccgacaag cgcttgagtg gatggatgg atcacaccc tcaatggtaa cacc aactac 180
gcacagaaat tccaggacag agt caccatt actaggaca ggtctatgag cacagcctac 240
atggagctga gcagcctgag atctgaggac acaggcatgt attactgtgc aagana 296

<210> SEQ ID NO 265
<211> LENGTH: 296
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 265
cagatgcagc tgggtcagtc tggggctgag gtgaagaaga ctgggtcc tc agtgaagg tt 60
tcctgc aagg cttccggata caccc tc acc taccgctacc tgcactgggt gcgacagg cc 120
ccccgacaag cgcttgagtg gatggatgg atcacaccc tcaatggtaa cacc aactac 180
gcacagaaat tccaggacag agt caccatt accaggaca ggtctatgag cacagcctac 240
atggagctga gcagcctgag atctgaggac acaggcatgt attactgtgc aagata 296

<210> SEQ ID NO 266
<211> LENGTH: 260
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 266
agaagactgg gtcctcagt aagg tttcct gcaaggcttc cggatacacc ttcaccc tacc 60
gtaccc tca ctgggtcgca caggcccca gacaaggcgc tgatggatg gatggatca 120
caccc tcaa tggtaaacacc aactacgcac agaaattcca ggacagagtc accattacca 180
gggacaggc tc tatgagcaca gcctacatgg agctgagcag cctgagatct gaggacacag 240
ccatgttata ctgtgc aaga 260

<210> SEQ ID NO 267
<211> LENGTH: 296
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 267
caggtgcagc tgggtcagtc tggggctgag gtgaagaaga ctggggcc tc agtgaagg tt 60
tcctgc aagg catctggata caccc tc acc agtactata tgcactgggt gcgacagg cc 120
cctggacaag ggcttgagtg gatggata atcaacccta gtgggttag cacaaggctac 180
gcacagaagt tccaggacag agt caccatg accaggaca cgtccacgag cacagtctac 240
atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagaga 296

<210> SEQ ID NO 268
<211> LENGTH: 296
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

```

-continued

<400> SEQUENCE: 268

caggtgcagc tggcagtc tgggctgag gtgaagaagc ctggggcctc agtgaaggtt	60
tccatcgaaagg cttctggata caccttcaac agtactata tgcactgggt gcgacaggcc	120
cctggacaag ggcttgagtg gatgggata atcaacccta gtgggtggtag cacaagctac	180
gcacagaagt tccaggcag agtcaccatg accagggaca cgtccacgag cacagtctac	240
atggagctga gcagectgag atctgaggac acggccgtgt attactgtgc gagaga	296

<210> SEQ ID NO 269

<211> LENGTH: 296

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 269

caggtgcagc tggcagtc tgggctgag gtgaagaagc ctggggcctc agtgaaggtt	60
tccatcgaaagg cttctggata caccttcaacc agtactata tgcactgggt gcgacaggcc	120
cctggacaag ggcttgagtg gatgggata atcaacccta gtgggtggtag cacaagctac	180
gcacagaagt tccaggcag agtcaccatg accagggaca cgtccacgag cacagtctac	240
atggagctga gcagectgag atctgaggac acggccgtgt attactgtgc tagaga	296

<210> SEQ ID NO 270

<211> LENGTH: 296

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 270

caaattgcagc tggcagtc tgggctgag gtgaagaagc ctggggcctc agtgaaggtc	60
tccatcgaaagg cttctggatt caccttact agtctgtgt tgcagtgggt gcgacaggct	120
cgtggacaac gccttgagtg gataggatgg atcgtcggtt gcagtggtaa cacaactac	180
gcacagaagt tccaggaaag agtcaccatt accagggaca tgtccacaag cacagctac	240
atggagctga gcagectgag atccgaggac acggccgtgt attactgtgc ggcaga	296

<210> SEQ ID NO 271

<211> LENGTH: 296

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 271

caaattgcagc tggcagtc tgggctgag gtgaagaagc ctggggcctc agtgaaggtc	60
tccatcgaaagg cttctggatt caccttact agtctgtgt tgcagtgggt gcgacaggct	120
cgtggacaac gccttgagtg gataggatgg atcgtcggtt gcagtggtaa cacaactac	180
gcacagaagt tccaggaaag agtcaccatt accagggaca tgtccacaag cacagctac	240
atggagctga gcagectgag atccgaggac acggccgtgt attactgtgc ggcaga	296

<210> SEQ ID NO 272

<211> LENGTH: 296

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 272

caggtgcagc tgccccagtc tgaggctgag gtaaagaagc ctggggcctc agtgaaggtc	60
tccatcgaaagg cttccggata caccttact tgcgtgttgcactgggtt gcaacaggcc	120

-continued

cctggacaag ggcttcaaag gatgagatgg atcacacttt acaatggtaa caccactat	180
gcaaagaagt tccagggcag agtcaccatt accagggaca tgtccctgag gacagcctac	240
ata gagactga gcagectgag atctgaggac tcggctgtgt attactggc aagata	296

<210> SEQ ID NO 273

<211> LENGTH: 296

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 273

cagggtgcagc tgggtgcagtc tggggctgag gtgaagaagc ctgggtcctc ggtgaaggc	60
tccctgcaagg cttctggagg caccttcagc agctatgcta tcagctgggt gcgacaggcc	120
cctggacaag ggcttgagtg gatgggaggg atcatcccta tccttggtag agcaaactac	180
gcacagaagt tccagggcag agtcacgatt accgcggacg aatccacgag cacagcctac	240
atggagactga gcagectgag atctgaggac acggccgtgt attactgtgc gagaga	296

<210> SEQ ID NO 274

<211> LENGTH: 294

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 274

cagggtccagc tggtgcaatc tggggctgag gtgaagaagc ctgggtcctc ggtgaaggc	60
tccctgcaagg cttctggagg caccttcagc agctatacta tcagctgggt gcgacaggcc	120
cctggacaag ggcttgagtg gatgggaagg atcatcccta tccttggtag agcaaactac	180
gcacagaagt tccagggcag agtcacgatt accgcggacg aatccacgag cacagcctac	240
atggagactga gcagectgag atctgaggac acggccgtgt attactgtgc gaga	294

<210> SEQ ID NO 275

<211> LENGTH: 275

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 275

cagggtgcagc tgggtgcagtc tggggctgag gtgaagaagc ctgggtcctc ggtgaaggc	60
tccctgcaagg cttctggagg caccttcagc agctatgcta tcagctgggt gcgacaggcc	120
cctggacaag ggcttgagtg gatgggaggg atcatcccta tccttggtag agcaaactac	180
gcacagaagt tccagggcag agtcacgatt accgcggacg aatccacgag cacagcctac	240
atggagactga gcagectgag atctgatgac acggc	275

<210> SEQ ID NO 276

<211> LENGTH: 296

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 276

cagggtccagc tggtgcaatc tggggctgag gtgaagaagc ctgggtcctc ggtgaaggc	60
tccctgcaagg cttctggagg caccttcagc agctatgcta tcagctgggt gcgacaggcc	120
cctggacaag ggcttgagtg gatgggaagg atcatcccta tccttggtag agcaaactac	180
gcacagaagt tccagggcag agtcacgatt accgcggacg aatccacgag cacagcctac	240
atggagactga gcagectgag atctgaggac acggccgtgt attactgtgc gagaga	296

-continued

```

<210> SEQ ID NO 277
<211> LENGTH: 294
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 277
caggtccagc tggtgcaagtc tggggctgag gtgaagaagc ctgggtcctc ggtgaaggc 60
tacctcaagg cttctggagg caccttcagc agctatgcta tcagctgggt gcgacaggcc 120
cctggacaag ggcttgagtg gatgggaggg atcatcccta tctttggtag accaaactac 180
gcacagaagt tccagggcag agtcacgatt accacggac aatccacgag cacagcctac 240
atggagctga gcagectgag atctgaggac acggccgtgt attactgtgc gagaga 294

<210> SEQ ID NO 278
<211> LENGTH: 296
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 278
caggtgcagc tggtgcaagtc tggggctgag gtgaagaagc ctgggtcctc ggtgaaggc 60
tacctcaagg cttctggagg caccttcagc agctatgcta tcagctgggt gcgacaggcc 120
cctggacaag ggcttgagtg gatgggaggg atcatcccta tctttggtag accaaactac 180
gcacagaagt tccagggcag agtcacgatt accgcggaca aatccacgag cacagcctac 240
atggagctga gcagectgag atctgaggac acggccgtgt attactgtgc gagaga 296

<210> SEQ ID NO 279
<211> LENGTH: 233
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 279
agaaggctgg gtcctcggtg aagggtctcct gcaaggcttc tggaggcacc ttctcagc 60
atgcataatcg ctgggtgcga caggccccctg gacaagggtc tgagtggatg ggaaggatca 120
tccctatctt tggtaacagca aactacgcac agaagttcca gggcagatgc acgattaccg 180
cgacacgaaatc cacgacgcaca gcctacatgg agctgagcag cctgagatct gag 233

<210> SEQ ID NO 280
<211> LENGTH: 296
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 280
caggtccagc tggtgcaatc tggggctgag gtgaagaagc ctgggtcctc ggtgaaggc 60
tacctcaagg cttctggagg caccttcagc agctatacta tcagctgggt gcgacaggcc 120
cctggacaag ggcttgagtg gatgggaggg atcatcccta tctttggtag accaaactac 180
gcacagaagt tccagggcag agtcacgatt accgcggaca aatccacgag cacagcctac 240
atggagctga gcagectgag atctgaggac acggccgtgt attactgtgc gagaga 296

<210> SEQ ID NO 281
<211> LENGTH: 296
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 281
caggtgcagc tggtgcaagtc tggggctgag gtgaagaagc ctgggtcctc ggtgaaggc 60

```

-continued

tccctgcagg cttctggagg caccttcagc agctatgcta tcagctgggt gcgacaggcc	120
cctggacaag ggcttgagtg gatgggaagg atcatcccta tccttggtat agcaaactac	180
gcacagaagt tccagggcag agtcacgatt accgcggaca aatccacgag cacagcctac	240
atggagctga gcagecttagatctgaggacc acggccgtgt attactgtgc gagaga	296

<210> SEQ ID NO 282

<211> LENGTH: 296

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 282

cagggtccagc tggtgcagtc tggggctgag gtgaagaagc ctgggtccctc agtgaaggc	60
tccctgcagg cttctggagg caccttcagc agctatgcta tcagctgggt gcgacaggcc	120
cctggacaag ggcttgagtg gatgggaagg atcatcccta tccttggtat agcaaactac	180
gcacagaagt tccagggcag agtcacgatt accgcggaca aatccacgag cacagcctac	240
atggagctga gcagecttagatctgaggacc acggccgtgt attactgtgc gagaga	296

<210> SEQ ID NO 283

<211> LENGTH: 296

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 283

cagggtccagc tggtgcagtc tggggctgag gtgaagaagc ctgggtccctc ggtgaaggc	60
tccctgcagg cttctggagg caccttcagc agctatgcta tcagctgggt gcgacaggcc	120
cctggacaag ggcttgagtg gatgggaagg atcatcccta tccttggtat agcaaactac	180
gcacagaagt tccagggcag agtcacgatt accgcggaca aatccacgag cacagcctac	240
atggagctga gcagecttagatctgaggacc acggccgtgt attactgtgc gagaga	296

<210> SEQ ID NO 284

<211> LENGTH: 296

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 284

cagggtccagc tggtgcagtc tggggctgag gtgaagaagc ctgggtccctc ggtgaaggc	60
tccctgcagg cttctggagg caccttcagc agctatgcta tcagctgggt gcgacaggcc	120
cctggacaag ggcttgagtg gatgggaagg atcatcccta tccttggtat agcaaactac	180
gcacagaagt tccagggcag agtcacgatt accgcggaca aatccacgag cacagcctac	240
atggagctga gcagecttagatctgaggacc acggccgtgt attactgtgc gagaga	296

<210> SEQ ID NO 285

<211> LENGTH: 296

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 285

cagggtccagc tggtgcagtc tggggctgag gtgaagaagc ctgggtccctc agtgaaggc	60
tccctgcagg cttctggagg caccttcagc agctatgcta tcagctgggt gcgacaggcc	120
cctggacaag ggcttgagtg gatgggaagg atcatcccta tccttggtat agcaaactac	180
gcacagaagt tccagggcag agtcacgatt accgcggaca aatccacgag cacagcctac	240
atggagctga gcagecttagatctgaggacc acggccgtgt attactgtgc gagaga	296

-continued

<210> SEQ ID NO 286
<211> LENGTH: 296
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 286

```
caggtgcagc tggtgcaagtc tggggcttag gtaagaaggc ctggggctc agtgaaggc 60
tcctgcaagg cttctggata caccttcacc agttatgata tcaactgggt gcgacaggcc 120
actggacaag ggcttgagtg gatgggatgg atgaacccta acagtggtaa cacaggctat 180
gcacagaagt tccagggcag agtcaccatg accaggaaca cctccataag cacagcctac 240
atggagctga gcagecttag atctgaggac acggccgtgt attactgtgc gagagg 296
```

<210> SEQ ID NO 287
<211> LENGTH: 296
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (136)..(136)
<223> OTHER INFORMATION: a, c, t or g
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (253)..(253)
<223> OTHER INFORMATION: a, c, t or g

<400> SEQUENCE: 287

```
caggttcagc tggtgcagcc tgggtccag gtgaagaaggc ctgggtccctc agtgaaggc 60
tcctgttagg cttccagata caccttcacc aaatacttta cacggtggtt gtgacaaaggc 120
cctggacaag ggcatnagtg gatgggatgg atcaaccctt acaacgataa cacacactac 180
gcacagacgt tctggggcag agtcaccatt accagtgaca ggtccatgag cacagcctac 240
atggagctga gcagecttag atccaaagac atggtcgtgt attactgtgt gagaga 296
```

<210> SEQ ID NO 288
<211> LENGTH: 260
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 288

```
ggaagtctgg ggcctcagtg aaagtctctt gtagtttttc tgggttacc atcaccagct 60
acggatataca ttgggtgcaa cagtcctctg gacaagggtt tgagtggatg ggatggatca 120
accctggcaa tggtagccca agctatgcca agaagttca gggcagatcc accatgacca 180
gggacatgtc cacaaccaca gcctacacag acctgaggcag cctgacatct gaggacatgg 240
ctgtgttatta ctatgcaaga 260
```

<210> SEQ ID NO 289
<211> LENGTH: 294
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 289

```
gaggtccagc tggcacatgtc tggggcttag gtaagaaggc ctggggctac agtggaaaatc 60
tcctgcaagg tttctggata caccttcacc gactactaca tgcactgggt gcaacaggcc 120
cctggaaaag ggcttgagtg gatgggactt gttgatcctg aagatggta aacaataaac 180
gcagagaagt tccagggcag agtcaccata accgcggaca cgtctacaga cacagcctac 240
```

-continued

atggagctga gcagecctgag atctgaggac acggccgtgt attactgtgc aaca	294
--	-----

<210> SEQ ID NO 290
<211> LENGTH: 233
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 290

agaagecctgg ggctacagtg aaaatctcct gcaaggtttc tggatacacc ttcaccgact	60
actacatgca ctgggtgcaa caggcccctg gaaaagggcgt tgagtggatg ggacttgg	120
atcctgaaga tggtaaaaca atatatgcag agaagttcca gggcagagtc accataaccg	180
cggacacggtc tacagacaca gcctacatgg agctgaggcag cctgagatct gag	233

<210> SEQ ID NO 291
<211> LENGTH: 294
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 291

caggtgcagc tgggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggc	60
tcctgcaagg cttctggata catttcacc gactactata tgcactgggt gcgacaggcc	120
cctggacaag agcttgggtg gatgggacgg atcaacccta acagtggtgg cacaaactat	180
gcacagaagt ttcagggcag agtcaccatg accagggaca cgtccatcag cacagcctac	240
acggagctga gcagcctgag atctgaggac acggccacgt attactgtgc gaga	294

<210> SEQ ID NO 292
<211> LENGTH: 296
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 292

caggtgcagc tgggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggc	60
tcctgcaagg cttctggata catttcacc gactactata tgcactgggt gcgacaggcc	120
cctggacaag agcttgggtg gatgggacgg atcaacccta acagtggtgg cacaaactat	180
gcacagaagt ttcagggcag agtcaccatg accagggaca cgtccatcag cacagcctac	240
acggagctga gcagcctgag atctgaggac acggccacgt attactgtgc gagaga	296

<210> SEQ ID NO 293
<211> LENGTH: 296
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 293

caggtgcagc tgggtgcagtc tggagctgag gtgaagaagc ctagagcctc agtgaaggc	60
tcctgcaagg cttctggta caccttacc agtactata tgcactgggt gtgacaggcc	120
cctgaacaag ggcttgagtg gatgggatgg atcaacactt acaatggtaa cacaaactac	180
ccacagaagc tccagggcag agtcaccatg accagagaca catccacgag cacagcctac	240
atggagctga gcaggcgtgag atctgacgac atggccgtgt attactgtgc gagaga	296

<210> SEQ ID NO 294
<211> LENGTH: 294
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 294

cagggtccaac tggtagtgc tggagctgag gtgaagaagc ctggggcctc agtgaaggc 60
 tcctgcaagg cttctggata caccttcacc gactactta tgaactggat gcgccaggcc 120
 cctggacaaa ggcttgagtg gatgggatgg atcaacgctg gcaatggtaa cacaatata 180
 tcacagaagc tccaggcag agtcaccatt accagggaca catctcgag cacagcctac 240
 atgcagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gaga 294

<210> SEQ ID NO 295

<211> LENGTH: 260

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 295

agaagcctgg ggcctcagtg aaggctcct gcaaggcttc tggatacacc ttcaccgact 60
 actttatgaa ctggatgcgc caggcccctg gacaaaggct tgagtggatg ggatggatca 120
 acgctggcaa tggtaacaca aaatattcac agaagctcca gggcagagtc accattacca 180
 gggacacatc tgcgagcaca gcctacatgc agctgagcag cctgagatct gaggacacgg 240
 ccgtgttata ctgtgcgaga 260

<210> SEQ ID NO 296

<211> LENGTH: 294

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 296

cagggtccaac tggtagtgc tggagctgag gtgaagaagc ctggggcctc agtgaaggc 60
 tcctgcaagg cttctggata caccttcacc agtactata tgaactggat gcgccaggcc 120
 cctggacaaag gcttggagtg gatgggatgg atcaacgctg gcaatggtaa cacaatgtat 180
 tcacagaagc tccaggcag agtcaccatt accagggaca catctcgag cacagcctac 240
 atgcagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gaga 294

<210> SEQ ID NO 297

<211> LENGTH: 294

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 297

caggaccagt tggtagtgc tggggctgag gtgaagaagc ctctgtcctc agtgaaggc 60
 tccttcaagg cttctggata caccttcacc aacaacttta tgcactgggt gtgacaggcc 120
 cctggacaaag gacttggagtg gatgggatgg atcaatgctg gcaatggtaa cacaacatata 180
 gcacagaagt tccaggcag agtcaccata accagggaca cgtccatgag cacagcctac 240
 acggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gaga 294

<210> SEQ ID NO 298

<211> LENGTH: 260

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 298

agaagcctgg ggcctcagtg aaggctcct gcaaggcttc tggatacacc ttcaccagct 60
 actgtatgca ctgggtgcac caggtccatg cacaaggcgt tgagtggatg ggatggatgt 120
 gccttagtga tggcagcaca agctatgcac agaagttcca ggccagagtc accataacca 180

-continued

gggacacatc catgagcaca gcctacatgg agctaaggcag tctgagatct gaggacacgg	240
ccatgttata ctgtgtgaga	260

<210> SEQ ID NO 299	
<211> LENGTH: 294	
<212> TYPE: DNA	
<213> ORGANISM: Homo sapiens	
<400> SEQUENCE: 299	
caggtacagc tggtgcaagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggc	60
tcctgcaggc cttctggata caccttcacc aactactgta tgcactgggt gcgccaggc	120
catgcacaag ggcttgagtg gatgggattg gtgtgcccta gtgatggcag cacaagctat	180
gcacaaaagt tccaggccag agtcaccata accagggaca catccatgag cacagcctac	240
atggagctaa gcagtctgag atctgaggac acggccatgt attactgtgt gaga	294

<210> SEQ ID NO 300	
<211> LENGTH: 296	
<212> TYPE: DNA	
<213> ORGANISM: Homo sapiens	
<400> SEQUENCE: 300	
caggtacagc tgatgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaggatc	60
tcctgcaggc cttctggata caccttcacc agtactgtt tgcactgggt gtgccaggcc	120
catgcacaag ggcttgagtg gatgggattg gtgtgcccta gtgatggcag cacaagctat	180
gcacagaagt tccaggccag agtcaccata accagggaca catccatggg cacagcctac	240
atggagctaa gcagcctgag atctgaggac acggccatgt attactgtgt gagaga	296

<210> SEQ ID NO 301	
<211> LENGTH: 301	
<212> TYPE: DNA	
<213> ORGANISM: Homo sapiens	
<400> SEQUENCE: 301	
caggtcacct tgaaggagtc tggcctgca ctggtgaaac ccacacagac cctcatgctg	60
acctgcacct tctctgggtt ctcactcagc acttctggaa tgggtgtggg ttagatctgt	120
cagccctcag caaaggccct ggagtggctt gcacacattt attagaatga taataaatac	180
tacagcccat ctctgaagag taggctcatt atctccaagg acacctccaa gaatgaagtg	240
gttctaacaag tgatcaacat ggacattgtg gacacagcca cacattactg tgcaaggaga	300
c	301

<210> SEQ ID NO 302	
<211> LENGTH: 301	
<212> TYPE: DNA	
<213> ORGANISM: Homo sapiens	
<400> SEQUENCE: 302	
caggtcacct tgaaggagtc tggcctgtg ctggtgaaac ccacagagac cctcacgctg	60
acctgcacct tctctgggtt ctcactcagc aatgctgaaat tgggtgtggg ctggatccgt	120
cagccccccag ggaaggccct ggagtggctt gcacacattt ttgcataatga cgaaaaatcc	180
tacagcccat ctctgaagag caggctcacc atctccaagg acacctccaa aagccagggt	240
gtccttacca tgaccaacat ggaccctgtg gacacagcca catattactg tgcaaggata	300
c	301

-continued

<210> SEQ ID NO 303
<211> LENGTH: 302
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 303

cagatcacct tgaaggagtc tggcctacg ctgggtgaaac ccacacagac cctcacgctg	60
acctgcacct tctctgggtt ctcactcagc actagtggag tgggtgtggg ctggatccgt	120
cagccccca gaaaggcccct ggagtggatt gcactcattt attggaatga tgataagcgc	180
tacagcccat ctctgaagag caggctcacc atcaccaagg acacctccaa aaaccaggtg	240
gtccttacaa tgaccaacat ggaccctgtg gacacagcca catattactg tgcacacaga	300
cc	302

<210> SEQ ID NO 304
<211> LENGTH: 124
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 304

actagtggag tgggtgtggg ctggatccgt cagccccca gaaaggcccct ggagtggctt	60
gcactcattt attggatga tgataagcgc tacagcccat ctctgaagag caggtcacc	120
atca	124

<210> SEQ ID NO 305
<211> LENGTH: 210
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 305

gtggtaaaa cccacacaga ccctcacgt gacctgcacc ttctctgggt tctcactcag	60
cactagtggatggatcgatccgt tcagccccca ggaaaggccc tggagtggctt	120
tgcactcattt tattggatg atgataagcgc ctacagccca tctctgaaga gcaggctcac	180
cattaccaag gacacccatccaa aaaaccaggt	210

<210> SEQ ID NO 306
<211> LENGTH: 297
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 306

cagatcacct tgaaggagtc tggcctacg ctgggtgaaac ccacacagac cctcacgctg	60
acctgcacct tctctgggtt ctcactcagc actagtggag tgggtgtggg ctggatccgt	120
cagccccca gaaaggcccct ggagtggattt gcactcattt attggaatga tgataagcgc	180
tacagcccat ctctgaagag caggctcacc atcaccaagg acacctccaa aaaccaggtg	240
gtccttacaa tgaccaacat ggaccctgtg gacacaggca catattactg tgtacgg	297

<210> SEQ ID NO 307
<211> LENGTH: 301
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 307

cagatcacct tgaaggagtc tggcctacg ctgggtgaaac ccacacagac cctcacgctg	60
---	----

-continued

acctgcacct tctctgggtt ctcactcagc actagtggag tgggtgtggg ctggatccgt	120
cagccccccag gaaaggccct ggagtggctt gcactcattt attggatga tgataagcgc	180
tacggcccat ctctgaagag caggctcacc atcaccaagg acacctccaa aaaccaggtg	240
gtccttacaa tgaccaacat ggaccctgtg gacacagcca catattactg tgcacacaga	300
c	301

<210> SEQ ID NO 308
<211> LENGTH: 300
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 308

cagatcacct tgaaggagtc tggcctacg ctggtaaaac ccacacagac cctcacgctg	60
acctgcacct tctctgggtt ctcactcagc actagtggag tgggtgtggg ctggatccgt	120
cagccccccag gaaaggccct ggagtggctt gcactcattt attggatga tgataagcgc	180
tacggcccat ctctgaagag caggctcacc atcaccaagg acacctccaa aaaccaggtg	240
gtccttacaa tgaccaacat ggaccctgtg gacacagcca catattactg tgcacacaga	300

<210> SEQ ID NO 309
<211> LENGTH: 294
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 309

cagatcacct tgaaggagtc tggcctacg ctggtgaaaac ccacacagac cctcacgctg	60
acctgcacct tctctgggtt ctcactcagc actagtggag tgggtgtggg ctggatccgt	120
cagccccccag gaaaggccct ggagtggctt gcactcattt attggatga tgataagcgc	180
tacagcccat ctctgaagag caggctcacc atcaccaagg acacctccaa aaaccaggtg	240
gtccttacaa tgaccaacat ggaccctgtg gacacagcca catattactg tgta	294

<210> SEQ ID NO 310
<211> LENGTH: 301
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 310

caggtcacct tgaaggagtc tggcctgcg ctggtgaaaac ccacacagac cctcacactg	60
acctgcacct tctctgggtt ctcactcagc actagtggaa tgcgtgtgag ctggatccgt	120
cagccccccag gaaaggccct ggagtggctt gcactcattt attggatga tgataagcgc	180
tacagcccat ctctgaagag caggctcacc atcaccaagg acacctccaa aaaccaggtg	240
gtccttacaa tgaccaacat ggaccctgtg gacacagcca catattactg tgcacacaga	300
c	301

<210> SEQ ID NO 311
<211> LENGTH: 301
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 311

caggtcacct tgaaggagtc tggcctacg ctggtgaaaac ccacacagac cctcacgctg	60
acctgcacct tctctgggtt ctcactcagc actagtggag tgggtgtggg ctggatccgt	120
cagccccccag gaaaggccct ggagtggctt gcactcattt attggatga tgataagcgc	180

-continued

tacggccat ctctgaagag caggctcacc atcaccaagg acacctccaa aaaccaggtg	240
gtccttacaa tgaccaacat ggaccctgtg gacacagcca catattactg tgcacacaga	300
c	301

<210> SEQ ID NO 312
<211> LENGTH: 297
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<400> SEQUENCE: 312

cagatcacct tgaaggagtc tggcctacg ctggtgaaac ccacacagac cctcacgctg	60
acctgcacct tctctgggtt ctcactcagc actagtggag tgggtgtggg ctggatccgt	120
cagccccccag gaaaggccct ggagtggctt gcactcattt attgggatga tgataagcgc	180
tacagcccat ctctgaagag caggctcacc atcaccaagg acacctccaa aaaccaggtg	240
gtccttacaa tgaccaacat ggaccctgtg gacacagcca catattactg tgcacagg	297

<210> SEQ ID NO 313
<211> LENGTH: 301
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<400> SEQUENCE: 313

caggtcacct tgagggagtc tggcctcgcg ctggtgaaac ccacacagac cctcacactg	60
acctgcacct tctctgggtt ctcactcagc actagtggaa tgtgtgtgag ctggatccgt	120
cagccccccag ggaaggccct ggagtggctt gcactcattt attgggatga tgataaatac	180
tacagcacat ctctgaagac caggctcacc atctccaagg acacctccaa aaaccaggtg	240
gtccttacaa tgaccaacat ggaccctgtg gacacagcca cgtattactg tgcacggata	300
c	301

<210> SEQ ID NO 314
<211> LENGTH: 290
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<400> SEQUENCE: 314

caggtcacct tgagggagtc tggcctcgcg ctggtgaaac ccacacagac cctcacactg	60
acctgcacct tctctgggtt ctcactcagc actagtggaa tgtgtgtgag ctggatccgt	120
cagccccccag ggaaggccct ggagtggctt gcactcattt attgggatga tgataaatac	180
tacagcacat ctctgaagac caggctcacc atctccaagg acacctccaa aaaccaggtg	240
gtccttacaa tgaccaacat ggaccctgtg gacacggccg tgtattactg	290

<210> SEQ ID NO 315
<211> LENGTH: 290
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<400> SEQUENCE: 315

caggtcacct tgaaggagtc tggcctcgcg ctggtgaaac ccacacagac cctcacactg	60
acctgcacct tctctgggtt ctcactcagc actagtggaa tgcgtgtgag ctggatccgt	120
cagccccccag ggaaggccct ggagtggctt gcacgcattt attgggatga tgataaattc	180
tacagcacat ctctgaagac caggctcacc atctccaagg acacctccaa aaaccaggtg	240

-continued

gtccttacaa tgaccaacat ggaccctgtg gacacggccg tgtattactg	290
--	-----

<210> SEQ ID NO 316
<211> LENGTH: 288
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 316

caggtcacct tgaaggagtc tggcctcgcg ctgggtgaaac ccacacagac cctcacactg	60
acctgcacct tctctgggtt ctcactcagc actagtggaa tgcgtgtgag ctggatccgt	120
cagccccccag ggaaggccct ggagtggctt gcacgcattt attggatga tgataaattc	180
tacagcacat ctctgaagac caggctcacc atctccaagg acacctccaa aaaccaggtg	240
gtccttacaa tgaccaacat ggaccctgtg gacacggccg cgtattac	288

<210> SEQ ID NO 317
<211> LENGTH: 237
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 317

tgcgctggtg aaacccacac agaccctcac actgaccctgc accttctctg gtttctcact	60
cagcactagt ggaatgcgtg cgagctggat ccgtcagccc ccagggaaagg ccctggagtg	120
gcttgcacgc attgattggg atgatgataa attctacagc acatctctga agaccaggct	180
caccatctcc aaggacacact cccaaaaacca ggtggtcctt acaatgacca acatgga	237

<210> SEQ ID NO 318
<211> LENGTH: 290
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 318

caggtcacct tgaaggagtc tggcctcgcg ctgggtgaaac ccacacagac cctcacactg	60
acctgcacct tctctgggtt ctcactcagc actagtggaa tgcgtgtgag ctggatccgt	120
cagccccccag ggaaggccct ggagtggctt gcacgcattt attggatga tgataaattc	180
tacagcacat ccctgaagac caggctcacc atctccaagg acacctccaa aaaccaggtg	240
gtccttacaa tgaccaacat ggaccctgtg gacacggccg tgtattactg	290

<210> SEQ ID NO 319
<211> LENGTH: 290
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 319

caggtcacct tgagggagtc tggcctcgcg ctgggtgaaac ccacacagac cctcacactg	60
acctgcacct tctctgggtt ctcactcagc actagtggaa tgcgtgtgag ctggatccgt	120
cagccccccgg ggaaggccct ggagtggctt gcactcattt attggatga tgataaatac	180
tacagcacat ctctgaagac caggctcacc atctccaagg acacctccaa aaaccaggtg	240
gtccttacaa tgaccaacat ggaccctgtg gacacggccg tgtattactg	290

<210> SEQ ID NO 320
<211> LENGTH: 290
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 320

-continued

caggtcacct tgagggagtc tggcctcgctgctgtgaaac ccacacagac cctcacactg	60
acctgcgcct tctctgggtt ctcaactcagc actagtggaa tgtgtgtgag ctggatccgt	120
cagccccccag ggaaggccct ggagtggctt gcacgcattt attggatga tgataaatac	180
tacagcacat ctctgaagac caggctcacc atctccaagg acacctccaa aaaccaggtg	240
gtccttacaa tgaccaacat ggaccctgtg gacacggccg tgtattactg	290

<210> SEQ ID NO 321

<211> LENGTH: 297

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 321

cagatcacct tgaaggagtc tggcctacg ctgggtgaaac ccacacagac cctcacgctg	60
acccgcaccc tctctgggtt ctcaactcagc actagtggaa tgtgtgtgag ctggatccgt	120
cagccccccag ggaaggccct ggagtggctt gcactcattt attggatga tgataaatac	180
tacagcacat ctctgaacac caggctcacc atctccaagg acacctccaa aaaccaggtg	240
gtccttacaa tgaccaacat ggaccctgtg gacacaggca catattactg tgtacgg	297

<210> SEQ ID NO 322

<211> LENGTH: 301

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 322

caggtcacct tgaaggagtc tggcctcgctgctgtgaaac ccacacagac cctcacactg	60
acctgcaccc tctctgggtt ctcaactcagc actagtggaa tgcgtgtgag ctggatccgt	120
cagccccccag ggaaggccct ggagtggatt gcacgcattt attggatga tgataaatac	180
tacagcacat ctctgaagac caggctcacc atctccaagg acacctccaa aaaccaggtg	240
gtccttacaa tgaccaacat ggaccctgtg gacacagcca cgtattactg tgcacggata	300
c	301

<210> SEQ ID NO 323

<211> LENGTH: 301

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 323

cagatcacct tgaaggagtc tggcctacg ctgggtgaaac ccacacagac cctcacgctg	60
acctgcaccc tctctgggtt ctcaactcagc actagtggaa tgtgtgtgag ctggatccgt	120
cagccccccag ggaaggccct ggagtggctt gcactcattt attggatga tgataaatac	180
tacagcacat ctctgaagac caggctcacc atctccaagg acacctccaa aaaccaggtg	240
gtccttacaa tgaccaacat ggaccctgtg gacacagcca catattactg tgcacacaga	300
c	301

<210> SEQ ID NO 324

<211> LENGTH: 301

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 324

caggtcacct tgagggagtc tggcctcgctgctgtgaaac ccacacagac cctcacactg	60
--	----

-continued

acctgcacct tctctgggtt ctcactcago actagtggaa tgtgtgtgag ctggatccgt	120
cagccccccag ggaaggccct ggagtggctt gcactcattt attggatga tgataaatac	180
tacagcacat ctctgaagac caggctcacc atctccaagg acacctccaa aaaccaggtg	240
gtccttacaa tgaccaacat ggaccctgtg gacacagcca cgtattatg tgacggata	300
c	301

<210> SEQ ID NO 325	
<211> LENGTH: 301	
<212> TYPE: DNA	
<213> ORGANISM: Homo sapiens	
<400> SEQUENCE: 325	
caggtcacct tgagggagtc tggcctcgct ctggtgaaac ccacacagac cctcacactg	60
acctgcacct tctctgggtt ctcactcago actagtggaa tgtgtgtgag ctggatccgt	120
cagccccccag ggaaggccct ggagtggctt gcactcattt attggatga tgataaatac	180
tacagcacat ctctgaagac caggctcacc atctccaagg acacctccaa aaaccaggtg	240
gtccttacaa tgaccaacat ggaccctgtg gacacagcca cgtattatg tgacggata	300
c	301

<210> SEQ ID NO 326	
<211> LENGTH: 298	
<212> TYPE: DNA	
<213> ORGANISM: Homo sapiens	
<400> SEQUENCE: 326	
caggtcacct tgaaggagtc tggcctcgct ctggtgaaac ccacagagac cctcacgctg	60
acctgcaccc tctctgggtt ctcactcago acttctggaa tgggtatgag ctggatccgt	120
cagccccccag ggaaggccct ggagtggctt gtcacattt ttttgaatga caaaaaatcc	180
tacagcacgt ctctgaagaa caggctcacc atctccaagg acacctccaa aagccaggtg	240
gtccttacca tgaccaacat ggaccctgtg gacacagcca cgtattactg tgcatgga	298

<210> SEQ ID NO 327	
<211> LENGTH: 296	
<212> TYPE: DNA	
<213> ORGANISM: Homo sapiens	
<400> SEQUENCE: 327	
caggtgcagc tgggggagtc ttgggtcaagc ctggagggtc cctgagactc	60
tcctgtgcag cctctggatt caccttcagt gactactaca tgagctggat ccgccaggct	120
ccagggaaagg ggctggagtg ggttcatac attagtagta gtggtagtac catataactac	180
gcagactctg tgaaggcccg attcaccatc tccagggaca acgccaagaa ctcactgtat	240
ctgcaaatga acagectgag agccgaggac acggccgtgt attactgtgc gagaga	296

<210> SEQ ID NO 328	
<211> LENGTH: 294	
<212> TYPE: DNA	
<213> ORGANISM: Homo sapiens	
<400> SEQUENCE: 328	
caggtgcagc tgggggagtc ttgggtcaagc ctggagggtc cctgagactc	60
tcctgtgcag cctctggatt caccttcagt gactactaca tgagctggat ccgccaggct	120
ccagggaaagg ggctggagtg ggttcatac attagtagta gtggtagtta cacaactac	180

-continued

gcagactctg tgaaggcccg attcaccatc tccagagaca acgccaagaa ctcactgtat	240
ctgcaaatga acagcctgag agccgaggac acggccgtgt attactgtgc gaga	294

<210> SEQ ID NO 329
<211> LENGTH: 293
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 329

gaggtgcate tgggggagtc tgggtacagc ctggggggc cctgagactc	60
tccctgtgcag cctctggatt caccttcagt aactacgaca tgcactgggt ccgccaagct	120
acaggaaaag gtctggagtg ggtctcagcc aatggtactg ctggtgacac atactatcca	180
ggctccgtga aggggcgatt caccatctcc agagaaaatg ccaagaactc cttgtatctt	240
caaataaca gcctgagagc cggggacacg gctgtgtatt actgtgcaag aga	293

<210> SEQ ID NO 330
<211> LENGTH: 293
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 330

gaggtgcate tgggggagtc tgggtacagc ctggggggc cctgagactc	60
tccctgtgcag cctctggatt caccttcagt aactacgaca tgcactgggt ccgccaagct	120
acaggaaaag gtctggagtg ggtctcagcc aatggtactg ctggtgacac atactatcca	180
ggctccgtga aggggcgatt caccatctcc agagaaaatg ccaagaactc cttgtatctt	240
caaataaca gcctgagagc cggggacacg gctgtgtatt actgtgcaag aga	293

<210> SEQ ID NO 331
<211> LENGTH: 291
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 331

gaggtgcagc tgggggagtc tgggggagcc ttggtaaagc ctggggggc cctgagactc	60
tccctgtgcag cctctggatt caccttcagt agctacgaca tgcactgggt ccgccaagct	120
acaggaaaag gtctggagtg ggtctcagct attggtactg ctggtgacac atactatcca	180
ggctccgtga agggccaatt caccatctcc agagaaaatg ccaagaactc cttgtatctt	240
caaataaca gcctgagagc cggggacacg gctgtgtatt actgtgcaag a	291

<210> SEQ ID NO 332
<211> LENGTH: 302
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 332

gaggtgcagc tgggggagtc tgggggagcc ttggtaaagc ctggggggc ccttagactc	60
tccctgtgcag cctctggatt cactttcagt aacgcctgga tgagctgggt ccgcccaggct	120
ccagggaaagg ggctggagtg gggtggccgt attaaaagca aaactgatgg tgggacaaca	180
gactacgctg cacccgtgaa aggccgatcc accatctcaa gagatgatcc aaaaaacacg	240
ctgtatctgc aaatgaacag cctgaaaacc gaggacacag ccgtgtatca ctgtaccaca	300
ga	302

-continued

<210> SEQ ID NO 333
<211> LENGTH: 302
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 333

gaggtgcagc tggggaggc ttggtaaacgc ctggggggc ctttagactc	60
tccctgtgcag cctctggatt cacttcagt aacgcctggc tgagctgggt ccgccaggct	120
ccagggaaagg ggctggaggc gggtggccgt attaaaagca aactgtatgg tgggacaaca	180
gactacgctg cacccgtgaa aggccatcc accatctcaa gagatgatcc aaaaaacacg	240
ctgtatctgc aaatgaacag cctgaaaacc gaggacacag ccgtgtatata ctgtaccaca	300
ga	302

<210> SEQ ID NO 334
<211> LENGTH: 302
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 334

gaggtgcagc tggggaggc ttggggaggc ttggtaaacgc ctggggggc ctttagactc	60
tccctgtgcag cctctggatt cacttcagt aacgcctggc tgagctgggt ccgccaggct	120
ccagggaaagg ggctggaggc gggtggccgt attgaaagca aactgtatgg tgggacaaca	180
gactacgctg cacccgtgaa aggccatcc accatctcaa gagatgatcc aaaaaacacg	240
ctgtatctgc aaatgaacag cctgaaaacc gaggacacag ccgtgtatata ctgtaccaca	300
ga	302

<210> SEQ ID NO 335
<211> LENGTH: 302
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 335

gaggtgcagc tggggaggc ttggggaggc ttggtaaacgc ctggggggc ctttagactc	60
tccctgtgcag cctctggatt cacttcagt aacgcctggc tgagctgggt ccgccaggct	120
ccagggaaagg ggctggaggc gggtggccgt attaaaagca aactgtatgg tgggacaaca	180
gactacgctg cacccgtgaa aggccatcc accatctcaa gagatgatcc aaaaaacacg	240
ctgtatctgc aaatgaacag tctgaaaacc gaggacacag ccgtgtatata ctgtaccaca	300
ga	302

<210> SEQ ID NO 336
<211> LENGTH: 302
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 336

gaggtgcagc tggggaggc ttggggaggc ttggtaaacgc ctggggggc ctttagactc	60
tccctgtgcag cctctggatt cacttcagt aacgcctggc tgagctgggt ccgccaggct	120
ccagggaaagg ggctggaggc gggtggccgt attaaaagca aactgtatgg tgggacaaca	180
aactacgctg cacccgtgaa aggccatcc accatctcaa gagatgatcc aaaaaacacg	240
ctgtatctgc aaatgaacag cctgaaaacc gaggacacag ccgtgtatata ctgtaccaca	300
ga	302

<210> SEQ ID NO 337
<211> LENGTH: 302
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 337

```

gaggtgcagc tggggaggc ttggtaaagc ctggggggc ccttagactc      60
tcctgtcgac cctctggttt cactttcagt aacgcctgaa tgaactgggt ccgccaggct    120
ccagggaaagg ggctggagtg ggctggccgt attaaaagca aaactgtatgg tgggacaaca    180
gactacgctg cacccgtgaa aggccatcc accatctcaa gagatgattc aaaaaacacg    240
ctgtatctgc aatgaacag cctgaaaacc gaggacacag ccgtgtatata ctgtaccaca    300
ga                                         302

```

<210> SEQ ID NO 338
<211> LENGTH: 302
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 338

```

gaggtgcagc tggggaggc ttggtaaagc ctggggggc ccttagactc      60
tcctgtcgac cctctggttt cactttcagt aacgcctgaa tgaactgggt ccgccaggct    120
ccagggaaagg ggctggagtg ggctggccgt attaaaagca aaactgtatgg tgggacaaca    180
gactacgctg cacccgtgaa aggccatcc accatctcaa gagatgattc aaaaaacacg    240
ctgtatctgc aatgaacag cctgaaaacc gaggacacag ccgtgtatata ctgtaccaca    300
ga                                         302

```

<210> SEQ ID NO 339
<211> LENGTH: 302
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 339

```

gaggtgcagc tggggaggc ttggtaaagc ctggggggc ccttagactc      60
tcctgtcgac cctctggatt cacttgcgt aacgcctgaa tgagctgggt ccgccaggct    120
ccagggaaagg ggctggagtg ggatggctgt attaaaagca aagctaatgg tgggacaaca    180
gactacgctg cacccgtgaa aggccatcc accatctcaa gagatgattc aaaaaacacg    240
ctgtatctgc aatgtatccg cctgaaaacc gaggacacgg ccgtgtatata ctgtaccaca    300
gg                                         302

```

<210> SEQ ID NO 340
<211> LENGTH: 296
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 340

```

gaggtacaac tggggaggc ttggtaaagc ctggggggc ccttagactc      60
tcctgtcgac cctctggatt cacccgtt aacagtgcata tgaactggc ccgcaggct    120
ccagggaaagg ggctggagtg ggtatgggt gttatggc atggcgttag gacgcactat    180
gtggactccg tgaagcccg attcatctc tccagagaca attccaggaa ctcccgtat    240
ctgcaaaaga acagacggag agccgaggac atggctgtgt attactgtgt gagaaa    296

```

-continued

<210> SEQ ID NO 341
<211> LENGTH: 296
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 341

gaggtgcagc tggggaggc ttggtagacg ctggggggc cctgagactc	60
tccctgtcgac cctctggatt caccttcaat aacagtgcata tgaactgggc ccgcaggct	120
ccaggaaagg ggctggaggc ggtatcggtt gtttagtttga atggcagtag gacgcactat	180
gtggactccg tgaaggcccg attcatcatc tccagagaca attccaggaa ctccctgtat	240
ctgcaaaaga acagacggag agccgaggac atggctgtgt attactgtgt gagaaa	296

<210> SEQ ID NO 342
<211> LENGTH: 296
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 342

acagtgcagc tggggaggc ttggtagacg ctggggggc cctgagactc	60
tccctgtcgac cctctggatt caccttcaat aacagtgcata tgaactgggc ccgcaggct	120
ccaggaaagg ggctggaggc ggtatcggtt gtttagtttga atggcagtag gacgcactat	180
gcagactctg tgaaggcccg attcatcatc tccagagaca attccaggaa ctccctgtat	240
cagcaaataa acagcctgag gcccggggac atggctgtgt attactgtgt gagaaa	296

<210> SEQ ID NO 343
<211> LENGTH: 296
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 343

gaggtgcagc tggggaggc ttggtagacg ctggggggc cctgagactc	60
tccctgtcgac cctctggatt caccttcatc gattatggca tggactgggt ccgcaggct	120
ccaggaaagg ggctggaggc ggtatcggtt attaatttggaa atggtggtag cacaggttat	180
gcagactctg tgaaggcccg attcatcatc tccagagaca acgccaagaa ctccctgtat	240
ctgcaaaatga acagcctgag agccgaggac acggccttgtt attactgtgc gagaga	296

<210> SEQ ID NO 344
<211> LENGTH: 296
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 344

gaggtgcagc tggggaggc ttggtagacg ctggggggc cctgagactc	60
tccctgtcgac cctctggatt caccttcaat agctatagca tgaactgggc ccgcaggct	120
ccaggaaagg ggctggaggc ggtatcggtt attagtagta tggatgttata cataactac	180
gcagactctg tgaaggcccg attcatcatc tccagagaca acgccaagaa ctccctgtat	240
ctgcaaaatga acagcctgag agccgaggac acggccttgtt attactgtgc gagaga	296

<210> SEQ ID NO 345
<211> LENGTH: 296
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 345

-continued

gaggtgcac	tggggaggc	ctggtaagc	ctggggggc	cctgagactc	60
tccctgtcg	actctggatt	cacccatgt	agctatagca	tgaactgggt	120
ccagggaaagg	ggctggagt	ggtctcatcc	attagtagta	gtagtagtta	180
gcagactcg	tgaaggccc	attcaccatc	tccagagaca	acgccaagaa	240
ctgcaaata	acagcctgag	agccgaggac	acggctgtgt	attactgtgc	296

<210> SEQ ID NO 346

<211> LENGTH: 302

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 346

gaggtgcac	tggggaggc	ttggtaac	ctggggggc	cctgagactc	60
tccctgtcg	actctggatt	cacccatgt	tactactaca	tgagcgggt	120
cccgaaaagg	ggctggat	ggtaggttc	attagaaaca	aagctaatt	180
gaatagacca	cgtctgtgaa	aggcagattc	acaatctcaa	gagatgattc	240
acctatctgc	aatgaagag	cctgaaaacc	gaggacacgg	ccgtgtat	300
ga					302

<210> SEQ ID NO 347

<211> LENGTH: 302

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 347

gaggtgcac	tggggaggc	ttggtaac	ctggggggc	cctgagactc	60
tccctgtcg	actctggatt	cacccatgt	tactactaca	tgagcgggt	120
cccgaaaagg	ggctggat	ggtaggttc	attagaaaca	aagctaatt	180
gaatagacca	cgtctgtgaa	aggcagattc	acaatctcaa	gagatgattc	240
acctatctgc	aatgaagag	cctgaaaacc	gaggacacgg	ccgtgtat	300
ga					302

<210> SEQ ID NO 348

<211> LENGTH: 296

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 348

gaggtgcac	tggggaggc	ttggtaac	ctggggggc	cctgagactc	60
tccctgtcg	actctggatt	cacccatgt	agctatgca	tgagctgggt	120
ccagggaaagg	ggctggagt	ggtctcagct	attagtggt	gtgggtgt	180
gcagactcc	tgaaggccc	tttcaccatc	tccagagaca	attccaagaa	240
ctgcaaata	acagcctgag	agccgaggac	acggccgtat	attactgtgc	296

<210> SEQ ID NO 349

<211> LENGTH: 296

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 349

gaggtgcac	tggggaggc	ttggtaac	ctggggggc	cctgagactc	60
-----------	-----------	----------	-----------	------------	----

-continued

tccctgtgcag cctctggatt cacctttagc agctatgcca tgagctgggt ccgccaggct	120
ccagggaaagg ggctggagtg ggtctcagct attagtggta gtgggtggtag cacataactac	180
ggagactccg tgaaggggccg gttcaccatc tcaagagaca attccaagaa cacgctgtat	240
ctgcaaatga acagectgag agccgaggac acggccgtat attactgtgc gaaaaga	296

<210> SEQ ID NO 350
<211> LENGTH: 294
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 350

gaggtgcagc tggtggagtc tgggggaggc ttggcacagc ctggggggtc cctgagactc	60
tccctgtgcag cctctggatt cacctttagc agctatgcca tgagctgggt ccgccaggct	120
ccagggaaagg ggctggagtg ggtctcagtt atttatacggt gttgttagtag cacataactat	180
gcagactccg tgaaggggccg gttcaccatc tccagagata attccaagaa cacgctgtat	240
ctgcaaatga acagectgag agccgaggac acggccgtat attactgtgc gaaa	294

<210> SEQ ID NO 351
<211> LENGTH: 296
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 351

gaggtgcagc tggtggagtc tgggggaggc ttggcacagc ctggggggtc cctgagactc	60
tccctgtgcag cctctggatt cacctttagc agctatgcca tgagctgggt ccgccaggct	120
ccagggaaagg ggctggagtg ggtctcagct attagtggta gtgggtggtag cacataactac	180
gcagactccg tgaaggggccg gttcaccatc tccagagata attccaagaa cacgctgtat	240
ctgcaaatga acagectgag agccgaggac acggccgtat attactgtgc gaaaaga	296

<210> SEQ ID NO 352
<211> LENGTH: 294
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 352

gaggtgcagc tggtggagtc tgggggaggc ttggcacagc ctggggggtc cctgagactc	60
tccctgtgcag cctctggatt cacctttagc agctatgcca tgagctgggt ccgccaggct	120
ccagggaaagg ggctggagtg ggtctcagct atttatacgca gttgttagtag cacataactat	180
gcagactccg tgaaggggccg gttcaccatc tccagagata attccaagaa cacgctgtat	240
ctgcaaatga acagectgag agccgaggac acggccgtat attactgtgc gaaa	294

<210> SEQ ID NO 353
<211> LENGTH: 296
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 353

gagatgcagc tggtggagtc tgggggaggc ttgcaaaagc ctgcgtggc cccgagactc	60
tccctgtgcag cctctcaatt caccttcagt agctactaca tgaactgtgt ccgccaggct	120
ccagggaaatg ggctggagtt ggtttgacaa gttaatccta atgggggttag cacataacctc	180
atagactccg gtaaggaccg attcaataacc tccagagata acgccaagaa cacacttcat	240
ctgcaaatga acagectgaa aaccgaggac acggccctct attagtgtac cagaga	296

<210> SEQ ID NO 354
<211> LENGTH: 296
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 354

gagatgcagc tggtgaggc tgggggaggc ttggcaaagc ctgcgtggc cccgagactc	60
tccctgtgcag cctctcaatt caccttcagt agctactaca tgaactgtgt ccgccaggct	120
ccagggaaatg ggctggagtt gggttgcacaa gttaatccta atggggtag cacataacctc	180
atagactccg gtaaggaccg attcaataacc tccagagata acgccaagaa cacacttcat	240
ctgcaaatga acagcctgaa aaccgaggac acggccctct attagtgtac cagaga	296

<210> SEQ ID NO 355
<211> LENGTH: 294
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 355

gagatgcagc tggtgaggc tgggggaggc ttggcaaagc ctgcgtggc cccgagactc	60
tccctgtgcag cctctcaatt caccttcagt agctactaca tgaactgtgt ccgccaggct	120
ccagggaaatg ggctggagtt gggttgcacaa gttaatccta atggggtag cacataacctc	180
atagactccg gtaaggaccg attcaataacc tccagagata acgccaagaa cacacttcat	240
ctgcaaatga acagcctgaa aaccgaggac acggccctgt attagtgtac caga	294

<210> SEQ ID NO 356
<211> LENGTH: 296
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 356

cagggtgcagc tggtgaggc tgggggaggc gtggtccagc ctggggaggc cctgagactc	60
tccctgtgcag cctctggatt caccttcagt agctatgcta tgcactgggt ccgccaggct	120
ccaggcaagg ggcttagatg ggtggcagtt atatcatatg atggaagtaa taaatactac	180
gcagactccg tgaaggcccg attcaccatc tccagagaca attccaagaa cacgtgttat	240
ctgcaaatga acagcctgag agctgaggac acggctgtgt attactgtgc gagaga	296

<210> SEQ ID NO 357
<211> LENGTH: 296
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 357

cagggtgcagc tggtgaggc tgggggaggc gtggtccagc ctggggggc cctgagactc	60
tccctgtgcag cgtctggatt caccttcagt agctatggca tgcactgggt ccgccaggct	120
ccaggcaagg ggctggagtg ggtggcattt atacggatg atggaagtaa taaatactat	180
gcagactccg tgaaggcccg attcaccatc tccagagaca attccaagaa cacgtgttat	240
ctgcaaatga acagcctgag agctgaggac acggctgtgt attactgtgc gaaaga	296

<210> SEQ ID NO 358
<211> LENGTH: 296
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

-continued

<400> SEQUENCE: 358

caggtgcagc tggggaggc gtgggcccagc ctggggaggc cctgagactc	60
tccctgtgcag cctctggatt caccttcagt agctatggca tgcactgggt ccgccaggct	120
ccaggcaagg ggctggaggc ggtggcagtt atatcatatg atgaaagtaa taaatactat	180
gcagactccg tgaaggggccg attcaccatc tccagagaca attccaagaa cacgctgtat	240
ctgcaaatga acagectgag agctgaggac acggctgtgt attactgtgc gagaga	296

<210> SEQ ID NO 359
<211> LENGTH: 296
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 359

caggtgcagc tggggaggc gtgggcccagc ctggggaggc cctgagactc	60
tccctgtgcag cctctggatt caccttcagt agctatggca tgcactgggt ccgccaggct	120
ccaggcaagg ggctggaggc ggtggcagtt atatcatatg atgaaagtaa taaatactac	180
gcagactccg tgaaggggccg attcaccatc tccagagaca attccaagaa cacgctgtat	240
ctgcaaatga acagectgag agctgaggac acggctgtgt attactgtgc gagaga	296

<210> SEQ ID NO 360
<211> LENGTH: 296
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 360

caggtgcagc tggggaggc gtgggcccagc ctggggaggc cctgagactc	60
tccctgtgcag cctctggatt caccttcagt agctatggca tgcactgggt ccgccaggct	120
ccaggcaagg ggcttagaggc ggtggcagtt atatcatatg atgaaagtaa taaatactac	180
gcagactccg tgaaggggccg attcaccatc tccagagaca attccaagaa cacgctgtat	240
ctgcaaatga acagectgag agctgaggac acggctgtgt attactgtgc gagaga	296

<210> SEQ ID NO 361
<211> LENGTH: 296
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 361

caggtgcagc tggggaggc gtgggcccagc ctggggaggc cctgagactc	60
tccctgtgcag cctctggatt caccttcagt agctatggca tgcactgggt ccgccaggct	120
ccaggcaagg ggcttagaggc ggtggcagtt atatcatatg atgaaagtaa taaatactac	180
gcagactccg tgaaggggccg attcaccatc tccagagaca attccaagaa cacgctgtat	240
ctgcaaatga acagectgag agctgaggac acggctgtgt attactgtgc gagaga	296

<210> SEQ ID NO 362
<211> LENGTH: 296
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 362

caggtgcagc tggggaggc gtgggcccagc ctggggaggc cctgagactc	60
tccctgtgcag cctctggatt caccttcagt agctatggca tgcactgggt ccgccaggct	120
ccaggcaagg ggcttagaggc ggtggcagtt atatcatatg atgaaagtaa taaatactac	180

-continued

gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat	240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagaga	296

<210> SEQ ID NO 363
<211> LENGTH: 294
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 363

caggtgcagc tgggtggactc tgggggaggc gtgggtccagc ctggggaggc cctgagactc	60
tccctgtgcag cctctggatt caccttcagt agctatgcta tgcactgggt ccggccaggct	120
ccaggcaagg ggcttagatg ggtggcagtt atatcatatg atggaagtaa taaatactac	180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat	240
ctgcaaatga acagcctgag agctgaggac acggctgtgt attactgtgc gagaga	294

<210> SEQ ID NO 364
<211> LENGTH: 296
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 364

caggtgcagc tgggtggagtc tgggggaggc gtgggtccagc ctggggaggc cctgagactc	60
tccctgtgcag cctctggatt caccttcagt agctatgcta tgcactgggt ccggccaggct	120
ccaggcaagg ggcttagatg ggtggcagtt atatcatatg atggaagtaa taaatactac	180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat	240
ctgcaaatga acagcctgag agctgaggac acggctgtgt attactgtgc gagaga	296

<210> SEQ ID NO 365
<211> LENGTH: 296
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 365

caggtgcagc tgggtggagtc tgggggaggc gtgggtccagc ctggggaggc cctgagactc	60
tccctgtgcag cctctggatt caccttcagt agctatgcta tgcactgggt ccggccaggct	120
ccaggcaagg ggcttagatg ggtggcagtt atatcatatg atggaagtaa taaatactac	180
acagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat	240
ctgcaaatga acagcctgag agctgaggac acggctgtgt attactgtgc gagaga	296

<210> SEQ ID NO 366
<211> LENGTH: 296
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 366

caggtgcagc tgggtggagtc tgggggaggc gtgggtccagc ctggggaggc cctgagactc	60
tccctgtgcag cctctggatt caccttcagt agctatgcta tgcactgggt ccggccaggct	120
ccaggcaagg ggcttagatg ggtggcagtt atatcatatg atggaagtaa taaatactac	180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat	240
ctgcaaatga acagcctgag agctgaggac acggctgtgt attactgtgc gagaga	296

<210> SEQ ID NO 367

-continued

<211> LENGTH: 296
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<400> SEQUENCE: 367

caggtgcagc tgggggaggc gtgggtccagc ctggggaggc cctgagactc	60
tccctgtgcag cctctggatt cacccatgt agctatggca tgcactgggt ccggccaggct	120
ccaggcaagg ggcttagagt ggtggcagtt atatcatatg atggaaagtaa taaatactac	180
gcagactccg tgaaggggccg attcaccatc tccagagaca attccaagaa cacgctgtat	240
ctgcaaatga acagcctgag agctgaggac acggctgtgt attactgtgc gagaga	296

<210> SEQ ID NO 368
<211> LENGTH: 296
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<400> SEQUENCE: 368

caggtgcagc tgggggaggc gtgggtccagc ctggggaggc cctgagactc	60
tccctgtgcag cctctggatt cacccatgt agctatggca tgcactgggt ccggccaggct	120
ccaggcaagg ggcttagagt ggtggcagtt atatcatatg atggaaagtaa taaatactac	180
gcagactccg tgaaggggccg attcaccatc tccagagaca attccaagaa caggctgtat	240
ctgcaaatga acagcctgag agctgaggac acggctgtgt attactgtgc gagaga	296

<210> SEQ ID NO 369
<211> LENGTH: 296
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<400> SEQUENCE: 369

caggtgcagc tgggggaggc gtgggtccagc ctggggaggc cctgagactc	60
tccctgtgcag cctctggatt cacccatgt agctatggca tgcactgggt ccggccaggct	120
ccaggcaagg ggcttagagt ggtggcagtt atatcatatg atggaaagtaa taaatactac	180
gcagactccg tgaaggggccg attcaccatc tccagagaca attccaagaa cacgctgtat	240
cttcaaatga acagcctgag agctgaggac acggctgtgt attactgtgc gagaga	296

<210> SEQ ID NO 370
<211> LENGTH: 296
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<400> SEQUENCE: 370

caggtgcagc tgggggaggc gtgggtccagc ctggggaggc cctgagactc	60
tccctgtgcag cctctggatt cacccatgt agctatggca tgcactgggt ccggccaggct	120
ccaggcaagg ggcttagagt ggtggcagtt atatcatatg atggaaagtaa taaatactac	180
gcagactccg tgaaggggccg attcaccatc tccagagaca attccaagaa cacgctgtat	240
ctgcaaatga acagcctgag agctgaggac acggctgtgt attactgtgc gagaga	296

<210> SEQ ID NO 371
<211> LENGTH: 296
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<400> SEQUENCE: 371

caggtgcagc tgggggaggc gtgggtccagc ctggggaggc cctgagactc	60
---	----

-continued

tcctgtcag cctctggatt caccttca	120
gactatgcta tgcactgggt ccgccaggcc	
ccaggcaagg ggcttagagt ggtggcagtt atatcatatg atggaagtaa taaatactac	180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat	240
ctgcaaatga acagcctgag agctgaggac acggctgtgt attactgtgc gagaga	296

<210> SEQ ID NO 372	
<211> LENGTH: 296	
<212> TYPE: DNA	
<213> ORGANISM: Homo sapiens	
<400> SEQUENCE: 372	
caggtgcagc tggtgagtc tgggggaggc gtggccagc ctgggaggc cctgagactc	60
tcctgtcag cctctggatt caccttca	120
gactatgcta tgcactgggt ccgccaggct	
ccaggcaagg ggcttagagt ggtggcagtt atatcatatg atggaagtaa taaatactac	180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat	240
ctgcaaatga acagcctgag agctgaggac acggctgtgt attactgtgc gagaga	296

<210> SEQ ID NO 373	
<211> LENGTH: 296	
<212> TYPE: DNA	
<213> ORGANISM: Homo sapiens	
<400> SEQUENCE: 373	
caggtgcagc tggtgagtc tgggggaggc gtggccagc ctgggaggc cctgagactc	60
tcctgtcag cctctggatt caccttca	120
gactatggca tgcactgggt ccgccaggct	
ccaggcaagg ggctggagtc ggtggcagtt atatcatatg atggaagtaa taaatactat	180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat	240
ctgcaaatga acagcctgag agctgaggac acggctgtgt attactgtgc gaaaga	296

<210> SEQ ID NO 374	
<211> LENGTH: 296	
<212> TYPE: DNA	
<213> ORGANISM: Homo sapiens	
<400> SEQUENCE: 374	
caggtgcagc tggtgagtc tgggggaggc gtggccagc ctgggaggc cctgagactc	60
tcctgtcag cgtctggatt caccttca	120
gactatggca tgcactgggt ccgccaggct	
ccaggcaagg ggctggagtc ggtggcagtt atatcatatg atggaagtaa taaatactac	180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat	240
ctgcaaatga acagcctgag agctgaggac acggctgtgt attactgtgc gagaga	296

<210> SEQ ID NO 375	
<211> LENGTH: 294	
<212> TYPE: DNA	
<213> ORGANISM: Homo sapiens	
<400> SEQUENCE: 375	
caggtgcagc tggtgagtc tgggggaggc gtggccagc ctgggaggc cctgagactc	60
tcctgtcag cctctggatt caccttca	120
gactatgcta tgcactgggt ccgccaggct	
ccaggcaagg ggctggagtc ggtggcagtt atatcatatg atggaagcaa taaatactac	180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat	240

-continued

ctgcaaatga acagcctgag agctgaggac acggctgtgt attactgtgc gaga	294
---	-----

<210> SEQ ID NO 376
<211> LENGTH: 296
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 376

caggtgcagc tgggggaggc gtgggtccagc ctggggaggc cctgagactc	60
tcctgtgcag cgtctggatt cacttcagt agctatgcta tgcactgggt ccgccaggct	120
ccaggcaagg ggctggagtg ggtggcagtt atatcatatg atggaagcaa taaatactac	180
gcagactccg tgaaggggccg attcaccatc tccagagaca attccaagaa cacgctgtat	240
ctgcaaatga acagcctgag agctgaggac acggctgtgt attactgtgc gaaaga	296

<210> SEQ ID NO 377
<211> LENGTH: 298
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 377

gaggtggagc tgatagagtc catagaggac ctgagacaac ctgggaagtt cctgagactc	60
tcctgtgttag cctctagatt cgccttcagt agcttctgaa tgagccgagt tcaccagtct	120
ccaggcaagg ggctggagtg agtaatagat ataaaagatg atggaagtca gatacaccat	180
gcagactctg tgaaggggcag attctccatc tccaaagaca atgctaagaa ctctctgtat	240
ctgcaaatga acactcagag agctgaggac gtggccgtgt atggctatac ataaggctc	298

<210> SEQ ID NO 378
<211> LENGTH: 296
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 378

caggtgcagc tgggggaggc gtgggtccagc ctggggaggc cctgagactc	60
tcctgtgcag cgtctggatt cacttcaagt agctatggca tgcactgggt ccgccaggct	120
ccaggcaagg ggctggagtg ggtggcagtt atatggatg atggaagtaa taaatactat	180
gcagactccg tgaaggggccg attcaccatc tccagagaca attccaagaa cacgctgtat	240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagaga	296

<210> SEQ ID NO 379
<211> LENGTH: 296
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 379

caggtacagc tgggggaggc gtgggtccagc ctggggaggc cctgagactc	60
tcctgtgcag cgtctggatt cacttcaagt agctatggca tgcactgggt ccgccaggct	120
ccaggcaagg ggctggagtg ggtggcagtt atatggatg atggaagtaa taaatactat	180
gcagactccg cgaaggggccg attcaccatc tccagagaca attccacgaa cacgctgttt	240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagaga	296

<210> SEQ ID NO 380
<211> LENGTH: 296
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

-continued

<400> SEQUENCE: 380

caggtgcagc tggtgaggc tgggggaggc gtggccagc ctggggaggc cctgagactc	60
tccctgtgcag cgtctggatt cacttcagt agctatggca tgcactgggt ccgcaggct	120
ccaggcaagg ggctggaggc ggtggcagtt atatggatg atggaaatggaa taaatactat	180
gcagactccg tgaaggggccg attcaccatc tccagagaca actccaagaa cacgctgtat	240
ctgcaaatga acagectgag agccgaggac acggctgtgt attactgtgc gaaaga	296

<210> SEQ ID NO 381

<211> LENGTH: 296
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 381

caggtgcagc tggtgaggc tgggggaggc gtggccagc ctggggaggc cctgagactc	60
tccctgtgcag cgtctggatt cacttcagt agctatggca tgcactgggt ccgcaggct	120
ccaggcaagg ggctggaggc ggtggcagtt atatcatatg atggaaatggaa taaatactat	180
gcagactccg tgaaggggccg attcaccatc tccagagaca attccaagaa cacgctgtat	240
ctgcaaatga acagectgag agccgaggac acggctgtgt attactgtgc gagaga	296

<210> SEQ ID NO 382

<211> LENGTH: 296
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 382

caggtgcagc tggtgaggc tgggggaggc gtggccagc ctggggaggc cctgagactc	60
tccctgtgcag cgtctggatt cacttcagt agctatggca tgcactgggt ccgcaggct	120
ccaggcaagg ggctggaggc ggtggcagtt atatcatatg atggaaatggaa taaatactat	180
gcagactccg tgaaggggccg attcaccatc tccagagaca attccaagaa cacgctgtat	240
ctgcaaatga acagectgag agccgaggac acggctgtgt attactgtgc gagaga	296

<210> SEQ ID NO 383

<211> LENGTH: 296
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 383

gaggtgcagc tggtgaggc tgggggaggc ttggtaacgc ctgggggatc cctgagactc	60
tccctgtgcag cctctggatt cacttcagt aacagtgaca tgaactgggt ccacatcggt	120
ccaggaaagg ggctggaggc ggtatcggtt gttagttggatggcgtatgacgcactat	180
gcagactctg tgaaggggccg attcatcatc tccagagaca attccagggaa cacccctgtat	240
ctgcaaacgaa atagcctgag ggccgaggac acggctgtgt attactgtgtt gagaaa	296

<210> SEQ ID NO 384

<211> LENGTH: 292
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 384

gaggtgcagc tggtgaggc tgggggaggc ttggtaacgc ctgggggatc cctgagactc	60
tccctgtgcag cctctggatt cacccgtcagt agcaatgaga tgagctggat ccgcaggct	120

-continued

ccagggagg ggctggagt ggtctcatcc attagtggtg gtagcacata ctacgcagac	180
tccaggaagg gcagattcac catctccaga gacaattcca agaacacgct gtatcttcaa	240
atgaacaacc tgagagctga gggcacggcc gcttattact gtgccagata ta	292
<210> SEQ ID NO 385	
<211> LENGTH: 292	
<212> TYPE: DNA	
<213> ORGANISM: Homo sapiens	
<400> SEQUENCE: 385	
gaggtgcagc tgggggagtc tgggggagtc ttgggtacagc ctggggggc cctgagactc	60
tccctgtgcag cctctggatt cacccgtca gaaatgaga tgagctggat ccggccaggct	120
ccagggagg ggctggagt ggtctcatcc attagtggtg gtagcacata ctacgcagac	180
tccaggaagg gcagattcac catctccaga gacaattcca agaacacgct gtatcttcaa	240
atgaacaacc tgagagctga gggcacggcc gcttattact gtgccagata ta	292
<210> SEQ ID NO 386	
<211> LENGTH: 298	
<212> TYPE: DNA	
<213> ORGANISM: Homo sapiens	
<400> SEQUENCE: 386	
gaagtgcagc tgggggagtc tgggggagtc gtgggtacagc ctggggggc cctgagactc	60
tccctgtgcag cctctggatt cacccgtca gttatccca tgcactgggt ccgtcaagct	120
ccggggagg gtctggagt ggtctctttt attagttggg atgggtggtag cacatactat	180
gcagactctg tgaaggccc attcaccatc tccagagaca acagaaaaa ctccctgtat	240
ctgcaaatga acagtctgag aactgaggac accgccttgtt attactgtgc aaaagata	298
<210> SEQ ID NO 387	
<211> LENGTH: 294	
<212> TYPE: DNA	
<213> ORGANISM: Homo sapiens	
<400> SEQUENCE: 387	
gaagtgcagc tgggggagtc tgggggagtc gtgggtacagc ctggggggc cctgagactc	60
tccctgtgcag cctctggatt cacccgtca gttatccca tgcactgggt ccgtcaagct	120
ccagggagg gtctggagt ggtctctttt attagttggg atgggtggtag cacatactat	180
gcagactctg tgaaggccc attcaccatc tccagagaca acagaaaaa ctccctgtat	240
ctgcaaatga acagtctgag aactgaggac accgccttgtt attactgtgc aaaa	294
<210> SEQ ID NO 388	
<211> LENGTH: 291	
<212> TYPE: DNA	
<213> ORGANISM: Homo sapiens	
<400> SEQUENCE: 388	
gaggatcagc tgggggagtc tgggggagtc ttgggtacagc ctggggggc cctgcaccc	60
tccctgtgcag cctctggatt cgccctca gctatgctc tgcactgggt tcggccggct	120
ccagggagg gtctggagt ggtatcagct attggtaactg gtggtgatac atactatgca	180
gactccgtga tggggccatt caccatctcc agagacaacc ccaagaagtc ctgttatctt	240
catatgaaca gcctgatagc tgaggacatg gctgtgtatt attgtgcaag a	291

-continued

<210> SEQ ID NO 389
<211> LENGTH: 293
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<400> SEQUENCE: 389

```

gaggatcagc tggtgaggc tgggtacagc ctggggggc cctgagaccc      60
tcctgtgcag cctctggatt cgccttca gactatgttc tgcaactgggt tcgcccggct    120
ccagggaaagg gtccggagtg ggtatca gtttccatcttca agagacaacg ccaagaagtc cttgttatctt    180
gactccgtga tggggccatt caccatctcc agagacaacg ccaagaagtc cttgttatctt    240
caaatgaaca gcctgata gtc tgaggacatg gctgtgtatt atttgcaag aga      293

```

<210> SEQ ID NO 390
<211> LENGTH: 282
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<400> SEQUENCE: 390

```

gaggatcagc tggtgaggc tgggtacagc ctggggggc cctgagaccc      60
tcctgtgcag cctctggatt cgccttca gactatgttc tgcaactgggt tcgcccggct    120
ccagggaaagg gtccggagtg ggtatca gtttccatcttca agagacaacg ccaagaagtc cttgttatctt    180
gactccgtga tggggccatt caccatctcc agagacaacg ccaagaagtc cttgttatctt    240
aaatgaacacg cctgata gtc tgaggacatg gctgtgtatt tg      282

```

<210> SEQ ID NO 391
<211> LENGTH: 296
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<400> SEQUENCE: 391

```

gagggtgcagc tggtgaggc tgggtacagc ctggggggc cctgagactc      60
tcctgtgcag cctctggatt cacccatca gactatagca tgaactgggt ccgccaggct    120
ccagggaaagg ggctggagtg ggtttccatca attagtagta gtagtagtac catataactac    180
gcagactctg tgaaggcccg attcaccatc tccagagaca atgccaagaa ctcactgtat    240
ctgcaa atga acagectgag agccgaggac acggctgtt attactgtgc gagaga      296

```

<210> SEQ ID NO 392
<211> LENGTH: 296
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<400> SEQUENCE: 392

```

gagggtgcagc tggtgaggc tgggtacagc ctggggggc cctgagactc      60
tcctgtgcag cctctggatt cacccatca gactatagca tgaactgggt ccgccaggct    120
ccagggaaagg ggctggagtg ggtttccatca attagtagta gtagtagtac catataactac    180
gcagactctg tgaaggcccg attcaccatc tccagagaca atgccaagaa ctcactgtat    240
ctgcaa atga acagectgag agccgaggac acggctgtt attactgtgc gagaga      296

```

<210> SEQ ID NO 393
<211> LENGTH: 296
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<400> SEQUENCE: 393

-continued

gaggtgcagc tggggaggc ttggtagc cttgggggtc cctgagactc	60
tccctgtcgac cttctggatt cacccatgt agttatgaaa tgaactgggt ccgccaggct	120
ccagggaaagg ggctggagtg ggtttcatac attagtagta gtggtagtac cataactac	180
gcagactctg tgaaggccg attcaccatc tccagagaca acgccaagaa ctcactgtat	240
ctgcaaatga acagcctgag agccgaggac acggctgttt attactgtgc gagaga	296

<210> SEQ ID NO 394

<211> LENGTH: 302

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 394

gaggtgcagc tggggaggc ttggtagc cttgggggtc cctgagactc	60
tccctgtacag cttctggatt cacccatgtt gattatgcta tgagctgggt ccgccaggct	120
ccagggaaagg ggctggagtg ggttaggttc attagaagca aagcttatgg tgggacaaca	180
gaatacaccg cgtctgtgaa aggtagattc accatctcaa gagatgggtc caaaagcatc	240
gcctatctgc aaatgaacag cctgaaaacc gaggacacag ccgtgtatata ctgtactaga	300
ga	302

<210> SEQ ID NO 395

<211> LENGTH: 302

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 395

gaggtgcagc tggggaggc ttggtagc cttgggggtc cctgagactc	60
tccctgtacag cttctggatt cacccatgtt gattatgcta tgagctgggt ccgccaggct	120
ccagggaaagg ggctggagtg ggttaggttc attagaagca aagcttatgg tgggacaaca	180
gaatacaccg cgtctgtgaa aggtagattc accatctcaa gagatgggtc caaaagcatc	240
gcctatctgc aaatgaacag cctgaaaacc gaggacacag ccgtgtatata ctgtactaga	300
ga	302

<210> SEQ ID NO 396

<211> LENGTH: 302

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 396

gaggtgcagc tggggaggc ttggtagc cttgggggtc cctgagactc	60
tccctgtacag cttctggatt cacccatgtt gattatgcta tgagctgggt ccgccaggct	120
ccagggaaagg ggctggagtg ggttaggttc attagaagca aagcttatgg tgggacaaca	180
gaatacaccg cgtctgtgaa aggtagattc accatctcaa gagatgggtc caaaagcatc	240
gcctatctgc aaatgaacag cctgaaaacc gaggacacag ccgtgtatata ctgtactaga	300
ga	302

<210> SEQ ID NO 397

<211> LENGTH: 302

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 397

gaggtgcagc tggggaggc ttggtagc cttgggggtc cctgagactc	60
---	----

-continued

tcctgtacag	tttctggatt	caccttttgtt	gattatgcta	tgagctgggt	ccgccaggct	120
ccagggaaagg	ggctggagtg	ggtaggtttc	attagaagca	aagcttatgg	tgggacaaca	180
gaataacgcgg	cgtctgtgaa	aggcagattc	accatctcaa	gagatgattc	caaaagcatc	240
gcctatctgc	aatgaacag	cctgaaaacc	gaggacacag	ccgtgttatta	ctgtactaga	300
ga						302

<210>	SEQ ID NO	398				
<211>	LENGTH:	302				
<212>	TYPE:	DNA				
<213>	ORGANISM:	Homo sapiens				
<400>	SEQUENCE:	398				
gaggtgcagc	ttgtggagtgc	tgggggaggc	ttggtaaagc	caggggggc	cctgagactc	60
tcctgtacag	tttctggatt	caccttttgtt	gattatgcta	tgagctgggt	ccgccaggct	120
ccagggaaagg	ggctggagtg	ggtaggtttc	attagaagca	aagcttatgg	tgggacaaca	180
gaataacgcgg	cgtctgtgaa	aggcagattc	accatctcaa	gagatgattc	caaaagcatc	240
gcctatctgc	aatgaacag	cctgaaaacc	gaggacacag	ccgtgttatta	ctgtactaga	300
ga						302

<210>	SEQ ID NO	399				
<211>	LENGTH:	296				
<212>	TYPE:	DNA				
<213>	ORGANISM:	Homo sapiens				
<400>	SEQUENCE:	399				
gaggtgcagc	ttgtggagtgc	tgggtgaggc	ttggtaacagc	ctggagggtc	cctgagactc	60
tcctgtgcag	cctctggatt	cacccatcgat	agtcctggaa	tgcactgggt	ctgccaggct	120
ccggagaagg	ggctggagtg	ggtagggccac	ataaaagtgtg	acggaagtga	gaaatactat	180
gttagactctg	tgaagggccg	attgaccatc	tccagagaca	atgccaagaa	ctccctctat	240
ctgcaagtga	acagecctgag	agctgaggac	atgaccgtgt	attactgtgt	gagagg	296

<210>	SEQ ID NO	400				
<211>	LENGTH:	294				
<212>	TYPE:	DNA				
<213>	ORGANISM:	Homo sapiens				
<400>	SEQUENCE:	400				
gaggtgcagc	ttgtggagtgc	tgggtgaggc	ttggtaacagc	ctggagggtc	cctgagactc	60
tcctgtgcag	cctctggatt	cacccatcgat	agtcctggaa	tgcactgggt	ctgccaggct	120
ccggagaagg	ggctggagtg	ggtagggccac	ataaaagtgtg	acggaagtga	gaaatactat	180
gttagactctg	tgaagggccg	attgaccatc	tccagagaca	atgccaagaa	ctccctctat	240
ctgcaagtga	acagecctgag	agctgaggac	atgaccgtgt	attactgtgt	gaga	294

<210>	SEQ ID NO	401				
<211>	LENGTH:	294				
<212>	TYPE:	DNA				
<213>	ORGANISM:	Homo sapiens				
<400>	SEQUENCE:	401				
gaggtgcagc	ttgtcgagtgc	tgggtgaggc	ttggtaacagc	ctggagggtc	cctgagactc	60
tcctgtgcag	cctctggatt	cacccatcgat	agtcctggaa	tgcactgggt	ctgccaggct	120

-continued

ccggagaagg ggctggagtg ggtggccgac ataaagtgtg acggaagtga gaaatactat 180
 gtagactctg tgaagggccg attgaccate tccagagaca atgccaagaa ctcccttat 240
 ctgcaagtga acagectgag agctgaggac atgaccgtgt attactgtgt gaga 294

<210> SEQ ID NO 402
 <211> LENGTH: 293
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 402
 gaggtgcagc tgggggagtc tggaggaggc ttgatccagc ctggggggc cctgagactc 60
 tcctgtgcag cctctgggtt caccgtcagt agcaactaca tgagctgggt ccggccaggct 120
 ccagggaaagg ggctggagtg ggtctcagtt atttatacgcg gtggtagcac atactacgca 180
 gactccgtga agggccgatt caccatctcc agagacaatt ccaagaacac gctgtatctt 240
 caaatgaaca gcctgagagc cgaggacacg gccgtgtatt actgtgcgag aga 293

<210> SEQ ID NO 403
 <211> LENGTH: 291
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 403
 gaggtgcagc tgggggagac tggaggaggc ttgatccagc ctggggggc cctgagactc 60
 tcctgtgcag cctctgggtt caccgtcagt agcaactaca tgagctgggt ccggccaggct 120
 ccagggaaagg ggctggagtg ggtctcagtt atttatacgcg gtggtagcac atactacgca 180
 gactccgtga agggccgatt caccatctcc agagacaatt ccaagaacac gctgtatctt 240
 caaatgaaca gcctgagagc cgaggacacg gccgtgtatt actgtgcgag a 291

<210> SEQ ID NO 404
 <211> LENGTH: 293
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 404
 gaggtgcagc tgggggagtc tggaggaggc ttgatccagc ctggggggc cctgagactc 60
 tcctgtgcag cctctgggtt caccgtcagt agcaactaca tgagctgggt ccggccaggct 120
 ccagggaaagg ggctggagtg ggtctcagtt atttatacgcg gtggtagcac atactacgca 180
 gactccgtga agggccgatt caccatctcc agagacaatt ccaagaacac gctgtatctt 240
 caaatgaaca gcctgagagc cgaggacacg gccgtgtatt actgtgcgag gga 293

<210> SEQ ID NO 405
 <211> LENGTH: 296
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 405
 gaggtacagc tgggggagtc tgaagaaaac caaagacaac ttgggggatc cctgagactc 60
 tcctgtgcag actctggatt aacttcagt agctactgaa tgagctcaga ttcccaagct 120
 ccagggaaagg ggctggagtg agtagtagat atatagttagg atagaagtca gctatgttat 180
 gcacaatctg tgaagagcag attcaccatc tccaaagaaa atgccaagaa ctcactctgt 240
 ttgcaaatga acagtctgag agcagagggc acggccgtgt attactgtat gtgagy 296

-continued

```

<210> SEQ ID NO 406
<211> LENGTH: 296
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 406

gaggtacagc tggggaggc tgaagaaaac caaagacaac ttgggggatc cctgagactc      60
tccctgtgcag actctggatt aaccttcagt agctactgaa tgagctcaga ttcccaggct     120
ccagggaaagg ggctggagtg agtagtagat atatagtacg atagaagtca gatatgttat     180
gcacaatctg tgaagagcag attcaccatc tccaaagaaa atgccaagaa ctcactccgt     240
ttgcaaatga acagtctgag agcagagggc acggccgtgt attactgtat gtgagg          296

<210> SEQ ID NO 407
<211> LENGTH: 296
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 407

gaggtacagc tggggaggc tgaagaaaac caaagacaac ttgggggatc cctgagactc      60
tccctgtgcag actctggatt aaccttcagt agctactgaa tgagctcaga ttcccaggct     120
ccagggaaagg ggctggagtg agtagtagat atatagtagg atagaagtca gctatgttat     180
gcacaatctg tgaagagcag attcaccatc tccaaagaaa atgccaagaa ctcactctgt     240
ttgcaaatga acagtctgag agcagagggc acggccgtgt attactgtat gtgagt          296

<210> SEQ ID NO 408
<211> LENGTH: 296
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 408

gaggtgcagc tggggaggc ttgggtccagc ctggggggatc cctgagactc      60
tccctgtgcag cctctggatt caccttcagt agctctgcta tgcaactgggt ccgccaggct    120
ccaaagaaagg gttttagtg ggtctcagtt attagtacaa gtgggtatac cgtaactctac    180
acagactctg tgaagggccg attcaccatc tccagagaca atgcccagaa ttcaactgtct    240
ctgcaaatga acagecctgag agcccgagggc acagttgtgt actactgtgt gaaaga          296

<210> SEQ ID NO 409
<211> LENGTH: 298
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 409

gaggtggagc tgatagaggc catagagggc ctgagacaac ttgggaaggc cctgagactc      60
tccctgtgtag cctctggatt caccttcagt agctactgaa tgagctgggt caatgagact    120
ctagggaaagg ggctggaggg agtaatagat gtaaaatatg atggaaagtca gatataccat    180
gcagactctg tgaagggccg attcaccatc tccaaagaca atgctaagaa ctcaccgtat    240
ctccaaacga acagtctgag agctgaggac atgaccatgc atggctgtac ataaggtt          298

<210> SEQ ID NO 410
<211> LENGTH: 294
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 410

```

-continued

gaggtggagc tgatagagtc catagaggc ctgagacaac ttggaaagt cctgagactc	60
tccctgttag cctctggatt caccttca gactactgaa tggactgggt caatgagact	120
ctagggagg ggctggagg agtaatagat gtaaaatatg atgaaagtca gatataccat	180
gcagactctg tgaagggcag attcaccatc tccaaagaca atgctaagaa ctcaccgtat	240
ctgcaaacgca acagtctgag agctgaggac atgaccatgc atggctgtac ataa	294

<210> SEQ ID NO 411

<211> LENGTH: 296

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 411

gaggtgcagc tggggaggc tggggaggc ttgggtccagc ctggggggtc cctgagactc	60
tccctgtgcag cctctggatt caccttca gactatgcta tgcactgggt ccgccaggct	120
ccagggagg gactgaaata tggggggtagt attagtagta atggggggtag cacatattat	180
gcagactctg tgaagggcag attcaccatc tccagagaca attccaagaa cacgctgtat	240
cttcaaatgg gcagcctgag agctgaggac atggctgtgt attactgtgc gagaga	296

<210> SEQ ID NO 412

<211> LENGTH: 296

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 412

gaggtgcagc tggggaggc tggggaggc ttgggtccagc ctggggggtc cctgagactc	60
tccctgtgcag cctctggatt caccttca gactatgcta tgcactgggt ccgccaggct	120
ccagggagg gactgaaata tggggggtagt attagtagta atggggggtag cacatattat	180
gcagactctg tgaagggcag attcaccatc tccagagaca attccaagaa cacgctgtat	240
cttcaaatgg gcagcctgag agctgaggac atggctgtgt attactgtgc gagaga	296

<210> SEQ ID NO 413

<211> LENGTH: 296

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 413

gaggtgcagc tggggaggc tggggaggc ttgggtccagc ctggggggtc cctgagactc	60
tccctgttcag cctctggatt caccttca gactatgcta tgcactgggt ccgccaggct	120
ccagggagg gactgaaata tggggggtagt attagtagta atggggggtag cacatactac	180
gcagacttcag tgaagggcag attcaccatc tccagagaca attccaagaa cacgctgtat	240
gtccaaatga gcagcctgag agctgaggac acggctgtgt attactgtgt gaaaga	296

<210> SEQ ID NO 414

<211> LENGTH: 296

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 414

caggtgcagc tggggaggc tggggaggc ttgggtccagc ctggggggtc cctgagactc	60
tccctgttcag cctctggatt caccttca gactatgcta tgcactgggt ccgccaggct	120
ccagggagg gactgaaata tggggggtagt attagtagta atggggggtag cacatactac	180
gcagacttcag tgaagggcag attcaccatc tccagagaca attccaagaa cacgctgtat	240

-continued

ctgcaaatga acagcctgag agctgaggac acggctgtgt attactgtgc gagaga 296

<210> SEQ ID NO 415

<211> LENGTH: 296

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 415

gaggtgcagc tggggagtc tggggggggc ttgggtccagc ctgggggggtc cctgagactc	60
tccctgttcag cctctggatt caccttcagt agctatgtca tgcaactgggt ccgccaggct	120
ccagggaaagg gactgaaata tggggggtagt attagtagta atgggggttag cacataactac	180
gactccgtga aggccgatt caccatctcc agagacaatt ccaagaacac gctgtatctt	240
caaataatga gcactgtcgag agctgaggac acggctgtgt attactgtgc gagaga	296

<210> SEQ ID NO 416

<211> LENGTH: 293

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 416

gaggtgcagc tggggagtc tggggggggc ttgggtccagc ctgggggggtc cctgagactc	60
tccctgttcag cctctggatt caccttcagt agcaactaca tgagctgggt ccgccaggct	120
ccagggaaagg ggctggagtg ggtctcagtt atttatagcg gtggtagcac atactacgca	180
gactccgtga aggccgatt caccatctcc agagacaatt ccaagaacac gctgtatctt	240
caaataatga gcactgtcgag cgaggacacg gctgtgtatt actgtgcgag aga	293

<210> SEQ ID NO 417

<211> LENGTH: 291

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 417

gaggtgcagc tggggagtc tggggggggc ttgggtccagc ctgggggggtc cctgagactc	60
tccctgttcag cctctggatt caccttcagt agcaactaca tgagctgggt ccgccaggct	120
ccagggaaagg ggctggagtg ggtctcagtt atttatagcg gtggtagcac atactacgca	180
gactccgtga aggccgatt caccatctcc agagacaatt ccaagaacac gctgtatctt	240
caaataatga gcactgtcgag tgaggacacg gctgtgtatt actgtgcgag a	291

<210> SEQ ID NO 418

<211> LENGTH: 293

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 418

gaggtgcagc tggggagtc tggggggggc ttgggtccagc ctgggggggtc cctgagactc	60
tccctgttcag cctctggatt caccttcagt agcaactaca tgagctgggt ccgccaggct	120
ccagggaaagg ggctggagtg ggtctcagtt atttatagct gtggtagcac atactacgca	180
gactccgtga aggccgatt caccatctcc agagacaatt ccaagaacac gctgtatctt	240
caaataatga gcactgtcgag tgaggacacg gctgtgtatt actgtgcgag aga	293

<210> SEQ ID NO 419

<211> LENGTH: 293

<212> TYPE: DNA

-continued

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 419

gaggtgcagc tggggaggc ttgggtccagc ctggggggtc cctgagactc	60
tccctgtgcag cctctggatt cacccgtca gacaactaca tgagctgggt ccgccaggct	120
ccagggaaagg ggctggaggc ggtctcgat atttatacg gtggtagcac atactacgca	180
gactccgtga aggccagatt caccatctcc agagacaatt ccaagaacac gctgtatctt	240
caaataatgaaca gcctgagagc cgaggacacg gctgtgtatt actgtgcgag aca	293

<210> SEQ ID NO 420

<211> LENGTH: 296

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 420

gaggtgcagc tggggaggc ttgggtccagc ctggggggtc cctgagactc	60
tccctgtgcag cctctggatt cacccgtca gacaactaca tgagctgggt ccgccaggct	120
ccagggaaagg ggctggaggc ggtggccaa acataaagcaag atggaaagtga gaaataactat	180
gtggactctg tgaaggcccg attcaccatc tccagagaca acgccaagaa ctcactgtat	240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagaga	296

<210> SEQ ID NO 421

<211> LENGTH: 294

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 421

gaggtgcagc tggggaggc ttgggtccagc ctggggggtc cctgagactc	60
tccctgtgcag cctctggatt cacccgtca gacaactaca tgagctgggt ccgccaggct	120
ccagggaaagg ggctggaggc ggtggccaa acataaagcaag atggaaagtga gaaataactat	180
gtggactctg tgaaggcccg attcaccatc tccagagaca acgccaagaa ctcactgtat	240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gaga	294

<210> SEQ ID NO 422

<211> LENGTH: 302

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 422

gaggtgcagc tggggaggc ttgggtccagc ctggggggtc cctgagactc	60
tccctgtgcag cctctggatt cacccgtca gacaactaca tgagctgggt ccgccaggct	120
cccgaaaagg ggctggaggc ggtggtttc attagaaaca aagctaattgg tggacaaca	180
gaatagacca cgtctgtgaa aggccatcc acaatctcaa gagatgattc caaaagcatc	240
acctatctgc aatgaacacg cctgagagcc gaggacacgg ccgtgtatata ctgtgcgaga	300
ga	302

<210> SEQ ID NO 423

<211> LENGTH: 302

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 423

gaggtgcagc tggggaggc ttgggtccagc ctggggggtc cctgagactc	60
--	----

-continued

tcctgtcag cctctggatt caccttca	gaccactaca tggactgggt ccgcaggct	120
ccagggaaagg ggctggagt ggttggccgt	actagaaaaca aagctaacag ttacaccaca	180
gaatacgcgc cgtctgtgaa aggcatatc	accatctcaa gagatgattc aaagaactca	240
ctgttatctgc aatgaacag cctgaaaacc	gaggacacgg ccgtgtat	300
ga		302

<210> SEQ ID NO 424

<211> LENGTH: 165

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 424

actttcagt accactacat ggactgggtc cgccaggctc	caggaaagg gctggagtgg	60
gttggccgta cttagaaacaa agctaacagc tacaccacag	aatacgcgc gtctgtgaaa	120
ggcagattca ccatctcaag agatgattca aagaactcac	tgtat	165

<210> SEQ ID NO 425

<211> LENGTH: 302

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 425

gaggtgcagc tgggggagtc tgggggaggc ttgggtccagc	ctgggggggtc cctgaaactc	60
tcctgtcag cctctgggtt caccttca	ggctctgcta tgcactgggt ccgcaggct	120
tccggaaag ggctggagt ggttggccgt	attagaagca aagctaacag ttacgcgaca	180
gcatatgctg cgtcggtgaa aggcatatc	accatctcca gagatgattc aaagaacacg	240
cgatctgc aatgaacag cctgaaaacc	gaggacacgg ccgtgtat	300
ca		302

<210> SEQ ID NO 426

<211> LENGTH: 302

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 426

gaggtgcagc tgggggagtc cgggggaggc ttgggtccagc	ctgggggggtc cctgaaactc	60
tcctgtcag cctctgggtt caccttca	ggctctgcta tgcactgggt ccgcaggct	120
tccggaaag ggctggagt ggttggccgt	attagaagca aagctaacag ttacgcgaca	180
gcatatgctg cgtcggtgaa aggcatatc	accatctcca gagatgattc aaagaacacg	240
cgatctgc aatgaacag cctgaaaacc	gaggacacgg ccgtgtat	300
ca		302

<210> SEQ ID NO 427

<211> LENGTH: 296

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 427

gaggtgcagc tgggggaggc tttagttcagc ctgggggggtc	cctgagactc	60
tcctgtcag cctctggatt caccttca	ggctactggta tgcactgggt ccgccaagct	120
ccagggaaagg ggctgggtgt	ggttctcacgt attaatagtg atgggagtag cacaagctac	180

-continued

gccccactccg tgaaggggccg attcaccatc tccagagaca acgccaagaa cacgctgtat	240
ctgcaaatga acagtctgag agccgaggac acggctgtgt attactgtgc aagaga	296

<210> SEQ ID NO 428
<211> LENGTH: 294
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 428

gaggtgcagc tgggggagtc tgggggaggc tttagttcagc ctggggggtc cctgagactc	60
tccctgtcgac cctctggatt caccttcaagt agctactgga tgcactgggt ccggcaagct	120
ccagggaaagg ggctgggtgt ggtctcacgt attaatagtg atgggagtag cacaacgtac	180
gccccactccg tgaaggggccg attcaccatc tccagagaca acgccaagaa cacgctgtat	240
ctgcaaatga acagtctgag agccgaggac acggctgtgt attactgtgc aaga	294

<210> SEQ ID NO 429
<211> LENGTH: 296
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 429

gaggtgcagc tgggggagtc cggggggaggc tttagttcagc ctggggggtc cctgagactc	60
tccctgtcgac cctctggatt caccttcaagt agctactgga tgcactgggt ccggcaagct	120
ccagggaaagg ggctgggtgt ggtctcacgt attaatagtg atgggagtag cacaacgtac	180
gccccactccg tgaaggggccg attcaccatc tccagagaca acgccaagaa cacgctgtat	240
ctgcaaatga acagtctgag agccgaggac acggctgtgt attactgtgc aaga	296

<210> SEQ ID NO 430
<211> LENGTH: 298
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 430

gaaagtgcagc tgggggagtc tgggtacagc ctggcaggc cctgagactc	60
tccctgtcgac cctctggatt caccttcatgatt gattatgcca tgcactgggt ccggcaagct	120
ccagggaaagg gcctggagtg ggtctcacgt attagttgaa atagttggtag cataggctat	180
gccccactctg tgaaggggccg attcaccatc tccagagaca acgccaagaa ctccctgtat	240
ctgcaaatga acagtctgag agctgaggac acggccttgtt attactgtgc aaaagata	298

<210> SEQ ID NO 431
<211> LENGTH: 288
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 431

gaggtgcagc tgggggagtc ttggtaacagc ctggggggtc cctgagactc	60
tccctgtcgac cctctggatt caccttcaagt agcaatgaga tgagctgggt ccggcaggct	120
ccagggaaagg gtctggagtg ggtctcacgtt attagttggtagt gtacacata ctacgcac	180
tccaggaagg gcagattcac catctccaga gacaattcca agaacacgct gcatcttcaa	240
atgaacagcc tgagagctga ggacacggct gtgtattact gtaagaaa	288

<210> SEQ ID NO 432
<211> LENGTH: 293

-continued

<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 432

gaggtgcagc tggggaggc ttggtaaagc ctgggggtc cctgagactc	60
tccctgtcgac cctctggatt caccttcagt gactactaca tgaactgggt ccgccaggct	120
ccagggaaagg ggctggagtg ggtctcatcc attagtagta gtagtaccat atactacgca	180
gactctgtga agggccgatt caccatctcc agagacaacg ccaagaactc actgttatctg	240
caaatgaaca gcctgagagc cgaggacacg gctgtgtatt actgtgcgag aga	293

<210> SEQ ID NO 433
<211> LENGTH: 293
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 433

gaggtgcagc tggggaggc ttggtaaagc ctgggggtc cctgagactc	60
tccctgtcgac cctctggatt caccttcagt gactactaca tgaactgggt ccgccaggct	120
ccagggaaagg ggctggagtg ggtctcatcc attagtagta gtagtaccat atactacgca	180
gactctgtga agggccgatt caccatctcc agagacaacg ccaagaactc actgttatctg	240
caaatgaaca gcctgagagc cgaggacacg gctgtttatt actgtgcgag aga	293

<210> SEQ ID NO 434
<211> LENGTH: 300
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 434

gaggtgcagc tggggaggc ttgggtccagc ctgggggttc tctgagactc	60
tcatgtcgac cctctggatt caccttcagt gaccactaca tgagctgggt ccgccaggct	120
caagggaaag ggctagagtt ggtaggtta ataagaaaca aagctaacag ttacacgaca	180
gaatatgctg cgtctgtgaa aggccagactt accatctcaa gagaggattc aaagaacacg	240
atgttatctgc aaatgagcaa cctgaaaacc gaggacttgg ccgtgtatata ctgtgctaga	300

<210> SEQ ID NO 435
<211> LENGTH: 300
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 435

gaggtgcagc tggggaggc ttgggtccagc ctgggggttc tctgagactc	60
tcatgtcgac cctctggatt caccttcagt gaccactaca tgagctgggt ccgccaggct	120
caagggaaag ggctagagtt ggtaggtta ataagaaaca aagctaacag ttacacgaca	180
gaatatgctg cgtctgtgaa aggccagactt accatctcaa gagaggattc aaagaacacg	240
ctgttatctgc aaatgagcaa cctgaaaacc gaggacttgg ccgtgtatata ctgtgctaga	300

<210> SEQ ID NO 436
<211> LENGTH: 300
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 436

gaggtgcagc tggggaggc ttgggtccagc ctgggggttc tctgagactc	60
--	----

-continued

tcatgtgcag cctctggatt cacttcagt gaccactaca tgagctgggt ccgccaggct	120
caaggaaaag ggcttagagtt ggttaggttataa agaaaca aagctaacag ttacacgaca	180
gaatatgctg cgtctgtgaa aggccagactt accatctcaa gagaggattc aaagaacacg	240
ctgttatctgc aatgagcag cctgaaaacc gaggacttgg ccgtgtatata ctgtgctaga	300

<210> SEQ ID NO 437

<211> LENGTH: 291

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 437

gagggttcagc tgggtcagtc tgggggaggc ttggtaacatc ctggggggtc cctgagactc	60
tccctgtgcag gctctggatt cacttcagt agctatgcta tgcactgggt tcgcccaggct	120
ccaggaaaag gtctggagtg ggtatcagct attggtaactg gtgggtggcac atactatgca	180
gactccgtga agggccgatt caccatctcc agagacaatg ccaagaactc cttgtatctt	240
caaataatgaaaca gcctgagagc cgaggacatg gctgtgtatt actgtgcaag a	291

<210> SEQ ID NO 438

<211> LENGTH: 291

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 438

gagggttcagc tgggtcagtc tgggggaggc ttggtaacagc ctggggggtc cctgagactc	60
tccctgtgcag gctctggatt cacttcagt agctatgcta tgcactgggt tcgcccaggct	120
ccaggaaaag gtctggagtg ggtatcagct attggtaactg gtgggtggcac atactatgca	180
gactccgtga agggccgatt caccatctcc agagacaatg ccaagaactc cttgtatctt	240
caaataatgaaaca gcctgagagc cgaggacatg gctgtgtatt actgtgcaag a	291

<210> SEQ ID NO 439

<211> LENGTH: 294

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 439

gagggtgcagc tggtagagtc tgggagagc ttggccccagc ctggggggta cctaaaactc	60
tccgggtgcag cctctggatt cacctcggt agctggtaca tgagctggat ccaccaggct	120
ccagggaagg gtctggagtg ggtctcatac attagtagta gtgggtttag cacaaactac	180
geagactctg tgaagggcag attcaccatc tccacagaca actcaaagaa cacgctctac	240
ctgcaaataatgaaaca acagecttgag agtggaggac acggccgtgtt attactgtgc aaga	294

<210> SEQ ID NO 440

<211> LENGTH: 294

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 440

gagggtgcagc tggtagagtc tgggagagc tttagtacagc ctggagggtc cctgagactc	60
tccctgtgcag cctctggatt cacttcagt agctactggta tgcactgggt ccgccaagct	120
ccagggaagg ggctgggtgtg ggtctcactgt attaatagtg atgggagtag cacaagctac	180
gcagactcca tgaagggcca attcaccatc tccagagaca atgctaagaa cacgctgtat	240
ctgcaaataatgaaaca acagtcttgag agtggaggac atggctgtgtt attactgtac taga	294

-continued

<210> SEQ ID NO 441
<211> LENGTH: 294
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 441

gaggtgcagc tggaggagtc tgggggaggc tttagtacagc ctggagggtc cctgagactc	60
tccctgtgcag cctctggatt caccttcagt agtactggaa tgcaactgggt ccggccatct	120
ccagggaaagg ggctgggtgtg agtctcacgt attaatagtg atgggagtag cacaagctac	180
geagactcct tgaagggccca attcaccatc tccagagaca atgctaagaa cacgctgtat	240
ctgcaaata gcaacatgtg acatgttgcg atggctgtgtt attactgtac taga	294

<210> SEQ ID NO 442
<211> LENGTH: 296
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 442

gaagtgcagc tgggtggagtc tgggggaggc ttgggtccagc ctgggggggtc cctgagactc	60
tccctgtgcag cctctgttatt caccttcagt aacagtgaca taaaactgggt cctctaggct	120
ccagggaaagg ggctggagtg ggtctcggtt attagttgga atggcggtaa gacgcactat	180
gtggactccg tgaagggccca attttccatc tccagagaca attccagcaa gtccctgtat	240
ctgcaaaaga acagacagag agccaaaggac atggccgtgtt attactgtgtt gagaaaa	296

<210> SEQ ID NO 443
<211> LENGTH: 294
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 443

gaggtgcagc tgggtggagtc tgggggaggc ttgggtccagc ctgggggggtc cctgagacac	60
tccctgtgcag cctctggatt caccttcagt aacagtgaca tgaactgggt cctctaggct	120
ccagggaaagg ggctggagtg ggtctcggtt attagttgga atggcggtaa gacgcactat	180
gtggactccg tgaagggccca atttaccatc tccagagaca attccagcaa gtccctgtat	240
ctgcaaaaga acagacagag agccaaaggac atggccgtgtt attactgtgtt gagaaaa	294

<210> SEQ ID NO 444
<211> LENGTH: 294
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 444

gaggtgcagc tgggtggagtc tgggggaggc ttgggtccagc ctgggggggtc cctgagacac	60
tccctgtgcag cctctggatt caccttcagt aacagtgaca tgaactgggt cctctaggct	120
ccagggaaagg ggctggagtg ggtctcggtt attagttgga atggcggtaa gacgcactat	180
gtggactccg tgaagggccca atttaccatc tccagagaca attccagcaa gtccctgtat	240
ctgcaaaaga acagacagag agccaaaggac atggccgtgtt attactgtgtt gagaaaa	294

<210> SEQ ID NO 445
<211> LENGTH: 292
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

-continued

<400> SEQUENCE: 445

gaggtgcagc tggggaggc ttggtagc cttgggggtc cctgagactg	60
tccctgtccag cctctggatt caccttcaat aaccactaca tgagctgggt ccggccaggct	120
ccagggaaagg gactggaggc gggttcatac attagtggtg atagtggta cacaaactac	180
gcagactctg tgaaggggccg attcaccatc tccagggaca acgccaataa ctcaccgtat	240
ctgcaaataa acagectgag agctgaggac acggctgtgt attactgtgt ga	292

<210> SEQ ID NO 446

<211> LENGTH: 292
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 446

gaggtgcagc tggggaggc ttggtagc cttgggggtc cctgagactc	60
tccctgtccag cctctggatt caccttcaat aaccactaca cgagctgggt ccggccaggct	120
ccagggaaagg gactggaggc gggttcatac agtagtggta atagtggta cacaaactac	180
gcagactctg tgaaggggccg attcaccatc tccagggaca acgccaagaa ctcactgtat	240
ctgcaaataa acagectgag agccgaggac acggctgtgt attactgtgt ga	292

<210> SEQ ID NO 447

<211> LENGTH: 296
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 447

caggtgcagc tgcaggaggc gggcccaggc ctgggtaaac cttcgacac cctgtccctc	60
acctgctgtc tctctggta ctccatcagc agtagtaact ggtggggctg gatccggcag	120
ccccccaggaa agggacttggc gtggatttttt tacatctatt atagtggag cacctactac	180
aacccgtccc tcaagagtcg agtcaccatc tcagtagaca cgtccaagaa ccagttctcc	240
ctgaagctga gctctgtgac cgccgtggac acggccgtgt attactgtgc gagaaa	296

<210> SEQ ID NO 448

<211> LENGTH: 296
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 448

caggtgcagc tgcaggaggc gggcccaggc ctgggtaaac cttcgacac cctgtccctc	60
acctgctgtc tctctggta ctccatcagc agtagtaact ggtggggctg gatccggcag	120
ccccccaggaa agggacttggc gtggatttttt tacatctatt atagtggag catctactac	180
aacccgtccc tcaagagtcg agtcaccatc tcagtagaca cgtccaagaa ccagttctcc	240
ctgaagctga gctctgtgac cgccgtggac acggccgtgt attactgtgc gagaaa	296

<210> SEQ ID NO 449

<211> LENGTH: 296
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 449

caggtgcagc tgcaggaggc gggcccaggc ctgggtaaac cttcgacac cctgtccctc	60
acctgctgtc tctctggta ctccatcagc agtagtaact ggtggggctg gatccggcag	120
ccccccaggaa agggacttggc gtggatttttt tacatctatt atagtggag cacctactac	180

-continued

aacccgtccc tcaagagtcg agtcaccatg tcagtagaca cgtccaagaa ccagttctcc 240
 ctgaagctga gctctgtgac cgccgtggac acggccgtgt attactgtgc gagaga 296

<210> SEQ ID NO 450
 <211> LENGTH: 294
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 450
 caggtgcagc tgcaggagtc gggcccgagga ctgggtgaagc cttcggacac cctgtccctc 60
 acctgctgtg tctctgggta ctccatcagc agtagtaact ggtggggctg gatccggcag 120
 cccccaggga agggacttggga gtggatttggg tacatctatt atagtgggag cacctactac 180
 aacccgtccc tcaagagtcg agtcaccatg tcagtagaca cgtccaagaa ccagttctcc 240
 ctgaagctga gctctgtgac cgccgtggac acggccgtgt attactgtgc gaga 294

<210> SEQ ID NO 451
 <211> LENGTH: 287
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 451
 caggtgcagc tgcaggagtc gggcccgagga ctgggtgaagc cttcggacac cctgtccctc 60
 acctgctgtg tctctgggta ctccatcagc agtagtaact ggtggggctg gatccggcag 120
 cccccaggga agggacttggga gtggatttggg tacatctatt atagtgggag catctactac 180
 aacccgtccc tcaagagtcg agtcaccatg tcagtagaca cgtccaagaa ccagttctcc 240
 ctgaagctga gctctgtgac cgccgtggac acggccgtgt attactgtgc 287

<210> SEQ ID NO 452
 <211> LENGTH: 299
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 452
 cagctgcagc tgcaggagtc cggctcagga ctgggtgaagc cttcacagac cctgtccctc 60
 acctgctgtg tctctgggta ctccatcagc agtgggttgtt actcctggag ctggatccgg 120
 cagccaccag ggaaggccct ggagtggatt gggtacatct atcatagtg gagcacctac 180
 tacaaccctgt ccctcaagag tcgagtcacc atatcagtag acaggtccaa gaaccatcc 240
 tccctgaagc tgagctctgt gaccgcccgcg gacacggcccg tgtattactg tgccagaga 299

<210> SEQ ID NO 453
 <211> LENGTH: 294
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 453
 cagctgcagc tgcaggagtc cggctcagga ctgggtgaagc cttcacagac cctgtccctc 60
 acctgctgtg tctctgggta ctccatcagc agtgggttgtt actcctggag ctggatccgg 120
 cagccaccag ggaaggccct ggagtggatt gggtacatct atcatagtg gagcacctac 180
 tacaaccctgt ccctcaagag tcgagtcacc atatcagtag acaggtccaa gaaccatcc 240
 tccctgaagc tgagctctgt gaccgctcgcg gacacggcccg tgtattactg tgcc 294

<210> SEQ ID NO 454

-continued

<211> LENGTH: 299
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<400> SEQUENCE: 454

```
cagctgcagc tgcaggagtc cggctcagga ctggtaaagc cttcacagac cctgtccctc      60
acctgcactg tctctgggtgg ctccatcagc agtggtggtt actccctggag ctggatccgg      120
cagccaccag ggaaggccct ggagtggatt gggagatctt attatagtgg gaggcactac      180
tacaaccctgt ccctcaagag tcgagtcacc atatccgttag acacgtccaa gaaccaggta      240
tccctgaagc tgagctctgt gaccgctgca gacacggctg tgtattactg tgcgagaca      299
```

<210> SEQ ID NO 455
<211> LENGTH: 227
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<400> SEQUENCE: 455

```
tctgggtggct ccatcagcag tgggtggttac tcctggagct ggatccggca gccaccagg      60
aaggggctgg agtggattgg gtacatctat catagtggga gcacctacta caaccctgtcc      120
ctcaagagtc gagtcaccat atcagtagac acgttccaaga accagttctc cctgaagctg      180
agctctgtga cccggcaga cacggccgtg tattactgtg cgagaga                      227
```

<210> SEQ ID NO 456
<211> LENGTH: 299
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<400> SEQUENCE: 456

```
caggtgcagc tgcaggagtc gggcccagga ctggtaaagc cttcacagac cctgtccctc      60
acctgcactg tctctgggtgg ctccatcagc agtggtgattt actactggag ttggatccgc      120
cagccccccag ggaaggccct ggagtggatt gggtacatctt attacagtgg gaggcactac      180
tacaaccctgt ccctcaagag tcgagttacc atatcagtag acacgtccaa gaaccaggta      240
tccctgaagc tgagctctgt gactgcccga gacacggccg tgtattactg tgccagaga      299
```

<210> SEQ ID NO 457
<211> LENGTH: 299
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<400> SEQUENCE: 457

```
caggtgcagc tgcaggagtc gggcccagga ctggtaaagc cttcgacac cctgtccctc      60
acctgcactg tctctgggtgg ctccatcagc agtggtgattt actactggag ttggatccgc      120
cagccccccag ggaaggccct ggagtggattt gggtacatctt attacagtgg gaggcactac      180
tacaaccctgt ccctcaagag tcgagttacc atatcagtag acacgtccaa gaaccaggta      240
tccctgaagc tgagctctgt gactgcccga gacacggccg tgtattactg tgccagaga      299
```

<210> SEQ ID NO 458
<211> LENGTH: 290
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<400> SEQUENCE: 458

```
caggtgcagc tgcaggagtc gggcccagga ctggtaaagc cttcacagac cctgtccctc      60
acctgcactg tctctgggtgg ctccatcagc agtggtgattt actactggag ttggatccgc      120
```

-continued

cagccccccag ggaagggcct ggagtggatt gggtacatct attacagtgg gagcacctac 180
 tacaaccgt ccctcaagag tcgagttacc atatcagtag acacgtccaa gaaccagttc 240
 tccctgaagc tgagctctgt gactgcccg gacacggccg tgtattactg 290

<210> SEQ ID NO 459
<211> LENGTH: 290
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 459

caggtgcagc tgcaggactc gggcccagga ctggtaagc cttcacagac cctgtccctc 60
 acctgcactg tctctggtgg ctccatcagc agtggtgatt actactggag ttggatccgc 120
 cagccccccag ggaagggcct ggagtggatt gggtacttctt attacagtgg gagcacctac 180
 tacaaccgt ccctcaagag tcgagttacc atatcagtag acacgtccaa gaaccagttc 240
 tccctgaagc tgagctctgt gactgcccg gacacggccg tgtattactg 290

<210> SEQ ID NO 460
<211> LENGTH: 228
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (54)..(54)
<223> OTHER INFORMATION: a, c, t or g

<400> SEQUENCE: 460

ctctggtggc tccatcagca gtggtgatta ctactggagt tggateccggc agcncccagg 60
 gaaggccctg gagtggattt ggtacatcta ttacagtgggg agcacctact acaacccgtc 120
 cctcaagagt cgagtcacca tatcagtaga cacgtccaag aaccagttct ccctgaagct 180
 gagctctgtg actgcccgag acacggccgt gtattactgt gccagaga 228

<210> SEQ ID NO 461
<211> LENGTH: 227
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 461

tctggtggct ccatcagcag tggtgattac tactggagtt ggtacccgcca gcacccagg 60
 aaggccctgg agtggattgg gtacatctat tacagtggga gcacctacta caacccgtcc 120
 ctcaagagtc gagttaccat atcagtagac acgtccaaga accagttctc cctgaagctg 180
 agctctgtga ctgcccaga cacggccgtg tattactgtg ccagaga 227

<210> SEQ ID NO 462
<211> LENGTH: 299
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 462

caggtgcagc tgcaggagtc gggcccagga ctggtaagc cttcacagac cctgtccctc 60
 acctgcactg tctctggtgg ctccatcagc agtggtggtt actactggag ctggatccgc 120
 cagcacccag ggaaggccct ggagtggatt gggtacatctt attacagtgg gagcacctac 180
 tacaaccgt ccctcaagag tcttagttacc atatcagtag acacgtctaa gaaccagttc 240
 tccctgaagc tgagctctgt gactgcccg gacacggccg tgtattactg tgcgagaga 299

-continued

<210> SEQ ID NO 463
<211> LENGTH: 299
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 463

caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcacagac cctgtccctc	60
acctgtactg tctctgggtgg ctccatcagc agtggtggtt actactggag ctggatccgc	120
cagcacccag ggaaggggct ggagtggatt gggtacatctt attacagtgg gagcacctac	180
tacaaccctg ccctcaagag tcgagttacc atatcagtag acacgtctaa gaaccagttc	240
tccctgaagc tgagctctgt gactgcccg gacacggccg tgtattactg tgcgagaga	299

<210> SEQ ID NO 464
<211> LENGTH: 299
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 464

caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcacagac cctgtccctc	60
acctgcactg tctctgggtgg ctccatcagc agtggtggtt actactggag ctggatccgc	120
cagcacccag ggaaggggct ggagtggatt gggtacatctt attacagtgg gagcacctac	180
tacaaccctg ccctcaagag tcgagttacc atatcagtag acacgtctaa gaaccagttc	240
tccctgaagc tgagctctgt gactgcccg gacacggccg tgtattactg tgcgagaga	299

<210> SEQ ID NO 465
<211> LENGTH: 294
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 465

caggtgcggc tgcaggagtc gggcccagga ctggtgaagc cttcacagac cctgtccctc	60
acctgcactg tctctgggtgg ctccatcagc agtggtggtt actactggag ctggatccgc	120
cagcacccag ggaaggggct ggagtggatt gggtacatctt attacagtgg gagcacctac	180
tacaaccctg ccctcaagag tcgagttacc atatcagtag acacgtctaa gaaccagttc	240
tccctgaagc tgagctctgt gactgcccg gacacggccg tgtattactg tgcg	294

<210> SEQ ID NO 466
<211> LENGTH: 291
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 466

caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcacagac cctgtccctc	60
acctgcactg tctctgggtgg ctccatcagc agtggtggtt actactggag ctggatccgc	120
cagcacccag ggaaggggct ggagtggatt gggtacatctt attacagtgg gagcacctac	180
tacaaccctg ccctcaagag tcgagttacc atatcagtag acacgtctaa gaaccagttc	240
tccctgaagc tgagctctgt gaccgcggac gccccgtgtt attactgtgc g	291

<210> SEQ ID NO 467
<211> LENGTH: 290
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 467

-continued

caggtgcagc tgcaggagtc gggcccagga ctgggtgaagc cttcacagac cctgtccctc	60
acctgcactg tctctggtgg ctccatcagc agtggtagtt actactggag ctggatccgc	120
cagcacccag ggaagggcct ggagtggatt gggtacatct attacagtgg gagcacctac	180
tacaaccctgt ccctcaagag tcgagttacc atatcagtag acacgtctaa gaaccagttc	240
tccctgaagc tgagctctgt gactgcccg gacacggccg tgtattactg	290

<210> SEQ ID NO 468

<211> LENGTH: 290

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 468

caggtgcagc tgcaggagtc gggcccagga ctgggtgaagc cttcacagac cctgtccctc	60
acctgcactg tctctggtgg atccatcagc agtggtagtt actactggag ctggatccgc	120
cagcacccag ggaagggcct ggagtggatt gggtacatct attacagtgg gagcacctac	180
tacaaccctgt ccctcaagag tcgagttacc atatcagtag acacgtctaa gaaccagttc	240
tccctgaagc tgagctctgt gactgcccg gacacggccg tgtattactg	290

<210> SEQ ID NO 469

<211> LENGTH: 290

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 469

caggtgcagc tgcaggagtc gggcccagga ctgggtgaagc cttcacagac cctgtccctc	60
acctgcactg tctctggtgg ctccatcagc agtggtagtt actactggag ctggatccgc	120
cagcacccag ggaagggcct ggagtggatt gggtacatct attacagtgg gagcacctac	180
tacaaccctgt ccctcaagag tcgagttacc atatcagtag acacgtccaa gaaccagttc	240
tccctgaagc tgagctctgt gactgcccg gacacggccg tgtattactg	290

<210> SEQ ID NO 470

<211> LENGTH: 290

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 470

caggtgcagc tgcaggagtc gggcccagga ctgggtgaagc cttcacagac cctgtccctc	60
acctgcactg tctctggtgg ctccatcagc agtggtagtt actactggag ctggatccgc	120
cagcacccag ggaagggcct ggagtggatt gggtacatct attacagtgg gagcacctac	180
tacaaccctgt ccctcaagag tcgagttacc atatcagtag acacgtccaa gaaccagttc	240
tccctgaagc tgagctctgt gaccgcccg gacacggccg tgtattactg	290

<210> SEQ ID NO 471

<211> LENGTH: 299

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 471

caggtgcagc tgcaggagtc gggcccagga ctgggtgaagc cttcacagac cctgtccctc	60
acctgcactg tctctggtgg ctccatcagc agtggtagtt actactggag ctggatccgc	120
cagcacccag ggaagggcct ggagtggatt gggtgcatactt attacagtgg gagcacctac	180

-continued

tacaaccgt ccctcaagag tcgagttacc atatcagtag acccgccaa gaaccagg	240
tccctgaagc cgagctctgt gactgccgac gacacggccg tggattactg tgccgagaga	299

<210> SEQ ID NO 472
<211> LENGTH: 293
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 472

caggtgcagc tacagcagt gggcgccagga ctgttgaagc cttcgagac cctgtccctc	60
acctgcgctg tctatggtgg gtccttcagt ggtaactact ggagctggat ccggccagccc	120
ccagggaaagg ggctggagtg gattggggaa atcaatcata gtggaaagcac caactacaac	180
ccgtccctca agagtcgagt caccatatca gtagacacgt ccaagaacca gttccctg	240
aagctgagct ctgtgaccgc cgccggacacg gctgtgtatt actgtgcgag agg	293

<210> SEQ ID NO 473
<211> LENGTH: 293
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 473

caggtgcagc tacaacagt gggcgccagga ctgttgaagc cttcgagac cctgtccctc	60
acctgcgctg tctatggtgg gtccttcagt ggtaactact ggagctggat ccggccagccc	120
ccagggaaagg ggctggagtg gattggggaa atcaatcata gtggaaagcac caactacaac	180
ccgtccctca agagtcgagt caccatatca gtagacacgt ccaagaacca gttccctg	240
aagctgagct ctgtgaccgc cgccggacacg gctgtgtatt actgtgcgag agg	293

<210> SEQ ID NO 474
<211> LENGTH: 284
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 474

caggtgcagc tacagcagt gggcgccagga ctgttgaagc cttcgagac cctgtccctc	60
acctgcgctg tctatggtgg gtccttcagt ggtaactact ggagctggat ccggccagccc	120
ccagggaaagg ggctggagtg gattggggaa atcaatcata gtggaaagcac caactacaac	180
ccgtccctca agagtcgagt caccatatca gtagacacgt ccaagaacca gttccctg	240
aagctgagct ctgtgaccgc cgccggacacg gccgtgtatt actg	284

<210> SEQ ID NO 475
<211> LENGTH: 293
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 475

caggtgcagc tacagcagt gggcgccagga ctgttgaagc cttcgagac cctgtccctc	60
acctgcgctg tctatggtgg gtccttcagt ggtaactact ggagctggat ccggccagccc	120
ccagggaaagg ggctggagtg gattggggaa atcaatcata gtggaaagcac caacaacaac	180
ccgtccctca agagtcgagc caccatatca gtagacacgt ccaagaacca gttccctg	240
aagctgagct ctgtgaccgc cgccggacacg gctgtgtatt actgtgcgag agg	293

<210> SEQ ID NO 476
<211> LENGTH: 293

-continued

<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 476

caggtgcagc tacagcagtg gggcgccagga ctgttgaagc cttcgagac cctgtccctc	60
acctgcgtg tctatggtgg gtccttcagt ggtaactact ggtagctggat ccggccagccc	120
ccaggaaagg ggctggagtg gattggggaa atcaatcata gtggaaagcac caacaacaac	180
ccgtccctca agagtcgagc caccatatca gttagacacgt ccaagaacca gtttccctg	240
aagctgagct ctgtgaccgc cgccggacacg gctgtgtatt actgtgcgag agg	293

<210> SEQ ID NO 477
<211> LENGTH: 284
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 477

caggtgcagc tacagcagtg gggcgccagga ctgttgaagc cttcgagac cctgtccctc	60
acctgcgtg tctatggtgg gtccttcagt ggtaactact ggtagctggat ccggccagccc	120
ccaggaaagg ggctggagtg gattggggaa atcaatcata gtggaaagcac caactacaac	180
ccgtccctca agagtcgagc caccatatca gttagacacgt ccaagaacca gtttccctg	240
aagctgggct ctgtgaccgc cgccggacacg gccgtgtatt actg	284

<210> SEQ ID NO 478
<211> LENGTH: 284
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 478

caggtgcagc tacagcagtg gggcgccagga ctgttgaagc cttcgagac cctgtccctc	60
acctgcgtg tctatggtgg gtccttcagt ggtaactact ggtagctggat ccggccagccc	120
ccaggaaagg ggctggagtg gattggggaa atcaaccata gtggaaagcac caactacaac	180
ccgtccctca agagtcgagc caccatatca gttagacacgt ccaagaacca gtttccctg	240
aagctgagct ctgtgaccgc cgccggacacg gccgtgtatt actg	284

<210> SEQ ID NO 479
<211> LENGTH: 288
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 479

caggtgcagc tacagcagtg gggcgccagga ctgttgaagc cttcgagac cctgtccctc	60
acctgcgtg tctatggtgg gaccttcagt ggtaactact ggtagctggat ccggccagccc	120
ccaggaaagg ggctggagtg gattggggaa atcaatcata gtggaaagcac caactacaac	180
ccgtccctca agagtcgagc caccatatca gttagacacgt ccaagaacca gtttccctg	240
aagctgagct ctgtgaccgc cgccggacacg gctgtgtatt actgtgcg	288

<210> SEQ ID NO 480
<211> LENGTH: 293
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 480

caggtgcagc tgccaggagtc gggcccgccagga ctgggtgaagc cttcacagac cctgtccctc	60
--	----

-continued

acctgcgtc tctatggtgg gtccttcagt ggttactact ggagctggat ccggccagccc	120
ccagggagg gactggagtg gattggggaa atcaatcata gtggaaagcac caactacaac	180
ccgtccctca agagtcgagt taccatatca gtagacacgt ctaagaacca gttctccctg	240
aagctgagct ctgtgactgc cgccggacacg gccgtgtatt actgtgcgag aga	293

<210> SEQ ID NO 481

<211> LENGTH: 293

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 481

caggtgcagc tgcaggagtc gggcccagga ctgggtgaagc cttcgagac cctgtccctc	60
acctgcgtc tctatggtgg gtccttcagt ggttactact ggagctggat ccggccagccc	120
ccagggagg gactggagtg gattggggaa atcaatcata gtggaaagcac caactacaac	180
ccgtccctca agagtcgaat caccatgtca gtagacacgt ccaagaacca gttctacctg	240
aagctgagct ctgtgaccgc cgccggacacg gccgtgtatt actgtgcgag ata	293

<210> SEQ ID NO 482

<211> LENGTH: 293

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 482

caggtgcagc tacagcagtg gggcgcagga ctgttgaagc cttcgagac cctgtccctc	60
acctgcgtc tctatggtgg gtccttcagt ggttactact ggagctggat ccggccagccc	120
ccagggagg ggctggagtg gattgggtat atctattata gtggagcac caacaacaac	180
ccgtccctca agagtcgagc caccatatca gtagacacgt ccaagaacca gttctccctg	240
aacctgagct ctgtgaccgc cgccggacacg gccgtgtatt gctgtgcgag aga	293

<210> SEQ ID NO 483

<211> LENGTH: 291

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 483

caggtgcagc tacagcagtg gggcgcagga ctgttgaagc cttcgagac cctgtccctc	60
acctgcgtc tctatggtgg gtccttcagt ggttactact ggagctggat ccggccagccc	120
ccagggagg ggctggagtg gattggggaa atcattcata gtggaaagcac caactacaac	180
ccgtccctca agagtcgagt caccatatca gtagacacgt ccaagaacca gttctccctg	240
aagctgagct ctgtgaccgc cgccggacacg gctgtgtatt actgtgcgag a	291

<210> SEQ ID NO 484

<211> LENGTH: 221

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 484

tatggtggtt ctttcagtgg ttactactgg agctggatcc gccagcccc aggaaagggg	60
ctggagtgga ttggggaaat caatcatagt ggaagcacca actacaaccc ctccctcaag	120
atgcgagtca ccatatcagt agacacgtcc aagaaccagt tttccctgaa gctgagctct	180
gtgaccggcg cggacacggc tgtgtattac tgtgcgagag g	221

-continued

<210> SEQ ID NO 485
<211> LENGTH: 299
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<400> SEQUENCE: 485

```
cagctgcagc tgcaggagtc gggcccagga ctgggtgaagc cttcgagac cctgtccctc      60
acctgcactg tctctggtgg ctccatcagc agtagtagtt actactgggg ctggatccgc      120
cagccccca ggaaggggct ggagtggatt gggagtatct attatagtgg gagcacctac      180
tacaaccctg ccctcaagag tcgagtccacc atatccgttag acacgtccaa gaaccaggta      240
tccctgaagc tgagctctgt gaccggcga gacacggctg tgtattactg tgcgagaca      299
```

<210> SEQ ID NO 486
<211> LENGTH: 299
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<400> SEQUENCE: 486

```
cagctgcagc tgcaggagtc gggcccagga ctgggtgaagc cttcgagac cctgtccctc      60
acctgcactg tctctggtgg ctccatcagc agtagtagtt actactgggg ctggatccgc      120
cagccccca ggaaggggct ggagtggatt gggagtatct attatagtgg gagcacctac      180
tacaaccctg ccctcaagag tcgagtccacc atatccgttag acacgtccaa gaaccacttc      240
tccctgaagc tgagctctgt gaccggcga gacacggctg tgtattactg tgcgagaga      299
```

<210> SEQ ID NO 487
<211> LENGTH: 290
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<400> SEQUENCE: 487

```
cagctgcagc tgcaggagtc gggcccagga ctgggtgaagc cttcgagac cctgtccctc      60
acctgcactg tctctggtgg ctccatcagc agtagtagtt actactgggg ctggatccgc      120
cagccccca ggaaggggct ggagtggatt gggagtatct attatagtgg gagcacctac      180
tacaaccctg ccctcaagag tcgagtccacc atatccgttag acacgtccaa gaaccaggta      240
tccctgaagc tgagctctgt gaccggcga gacacggccg tgtattactg tgcgagaga      290
```

<210> SEQ ID NO 488
<211> LENGTH: 196
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<400> SEQUENCE: 488

```
gtcccatcag cagtagtagt tactactgg gctggatccg ccagccccca gggaggggc      60
tggagtggat tgggagttatc tattatagtg ggagcaccta ctacaaccctg tccctcaaga      120
gtcgagtccatcatatccgtta gacacgtccaa agaaccaggta ctccctgaag ctgagctctg      180
tgaccggccgc ggacac      196
```

<210> SEQ ID NO 489
<211> LENGTH: 294
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<400> SEQUENCE: 489

```
cagctgcagc tgcaggagtc gggcccagga ctgggtgaagc cttcgagac cccgtccctc      60
```

-continued

acctgcactg tctctggtgg ctccatcagc agtagtagtt actactgggg ctggatccgc	120
cagcccccaag ggaaggggct ggagtggatt gggagtatct attatagtgg gagcacctac	180
tacaaccctgt ccctcaagag tcgagtcacc atatccgtag acacgtccaa gaaccagttc	240
tccctgaagc tgagctctgt gaccgccgca gacacggctg tgtattactg tgcg	294

<210> SEQ ID NO 490

<211> LENGTH: 299

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 490

cggctgcagc tgcaggagtc gggcccagga ctggtaagc cttcgagac cctgtccctc	60
acctgcactg tctctggtgg ctccatcagc agtagtagtt actactgggg ctggatccgc	120
cagcccccaag ggaaggggct ggagtggatt gggagtatct attatagtgg gagcacctac	180
tacaaccctgt ccctcaagag tcgagtcacc atatccgtag acacgtccaa gaaccagttc	240
tccctgaagc tgagctctgt gaccgccgca gacacggctg tgtattactg tgcgagaga	299

<210> SEQ ID NO 491

<211> LENGTH: 299

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 491

cagctgcagc tgcaggagtc gggcccagga ctggtaagc cttcgagac cctgtccctc	60
acctgcactg tctctggtgg ctccatcagc agtagtagtt actactgggg ctggatccgc	120
cagcccccaag ggaaggggct ggagtggatt gggagtatct attatagtgg gagcacctac	180
tacaaccctgt ccctcaagag tcgagtcacc atatccgtag acacgtccaa gaaccagttc	240
tccctgaagc tgagctctgt gaccgccgca gacacggctg tgtattactg tgcgagaga	299

<210> SEQ ID NO 492

<211> LENGTH: 296

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 492

caggtgcagc tgcaggagtc gggcccagga ctggtaagc ctccggggac cctgtccctc	60
acctgcgctg tctctggtgg ctccatcagc agtagtaact ggtggagttt ggtccgcag	120
cccccaggga agggggcttga gtggattttt gaaatctatc atagtgggag caccaactac	180
aaccctgtccc tcaagagtcg agtcaccata tcagtagaca agtccaagaa ccagttctcc	240
ctgaagctga gctctgtgac cgccgcggac acggccgtgtt attactgtgc gagaga	296

<210> SEQ ID NO 493

<211> LENGTH: 296

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 493

caggtgcagc tgcaggagtc gggcccagga ctggtaagc ctccggggac cctgtccctc	60
acctgcgctg tctctggtgg ctccatcagc agtagtaact ggtggagttt ggtccgcag	120
cccccaggga agggggcttga gtggattttt gaaatctatc atagtgggag caccaactac	180
aaccctgtccc tcaagagtcg agtcaccata tcagtagaca agtccaagaa ccagttctcc	240
ctgaagctga gctctgtgac cgccgcggac acggccgtgtt attactgtgc gagaga	296

-continued

<210> SEQ_ID NO 494
<211> LENGTH: 287
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 494

caggtgcagc tgcaggagtc	gggcccagga ctggtgaagc	ctccggggac cctgtccctc	60
acctgctgctg tctctgggtgg	ctccatcagc agtagtaact	ggtgaggatgg ggtccgcag	120
cccccaggaa aggggctgga	gtggattttggg gaaatctatc	atagtggggag caccaactac	180
aaccctgtccc tcaagagtcg	agtccaccata tcagtagaca	agtccaagaa ccagttctcc	240
ctgaagctga gctctgtgac	cgccgcggac acggccgtgt	attactg	287

<210> SEQ_ID NO 495
<211> LENGTH: 287
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 495

caggtgcagc tgcaggagtc	gggcccagga ctggtgaagc	ctccggggac cctgtccctc	60
acctgctgcta tctctgggtgg	ctccatcagc agtagtaact	ggtgaggatgg ggtccgcag	120
cccccaggaa aggggctgga	gtggattttggg gaaatctatc	atagtggggag caccaactac	180
aaccctgtccc tcaagagtcg	agtccaccata tcagtagaca	agtccaagaa ccagttctcc	240
ctgaagctga gctctgtgac	cgccgcggac acggccgtgt	attactg	287

<210> SEQ_ID NO 496
<211> LENGTH: 287
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 496

caggtgcagc tgcaggagtt	gggcccagga ctggtgaagc	ctccggggac cctgtccctc	60
acctgctgctg tctctgggtgg	ctccatcagc agtagtaact	ggtgaggatgg ggtccgcag	120
cccccaggaa aggggctgga	gtggattttggg gaaatctatc	atagtggggag caccaactac	180
aaccctgtccc tcaagagtcg	agtccaccata tcagtagaca	agtccaagaa ccagttctcc	240
ctgaagctga gctctgtgac	cgccgcggac acggccgtgt	attactg	287

<210> SEQ_ID NO 497
<211> LENGTH: 224
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (59)..(61)
<223> OTHER INFORMATION: a, c, t or g

<400> SEQUENCE: 497

tctgggtggct ccatcagcag	tagtaactgg tggagttggg	tccgccagcc cccagggann	60
nggctggagt ggattggggaa	aatcttatcat agtggggagca	coaactacaa cccgtccctc	120
aagagtgcag tcaccatgtc	agttagacacg tccaagaacc	agttctccct gaagctgagc	180
tctgtgaccg ccgcggacac	ggccgtgtat tactgtgcga	gaga	224

<210> SEQ_ID NO 498
<211> LENGTH: 293
<212> TYPE: DNA

-continued

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 498

caggtgcagc tgcaggagtc gggcccagga ctggtaa	60
cttcggagac cctgtccctc	
acatcgactg tctctgggtgg ctccatcagt agttactact	120
ggagctggat ccggcagccc	
gccccggaaagg gactggagtg atttgggat atctatacca	180
gtgggagcac caactacaac	
ccctccctca agagtcgagt caccatgtca gtagacacgt	240
ccaagaacca gttctccctg	
aagctgagct ctgtgaccgc cgccggacacg gccgtgtatt	293
actgtgcgag	

<210> SEQ ID NO 499

<211> LENGTH: 296

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 499

caggtgcagc tgcaggagtc gggcccagga ctggtaa	60
cttcggagac cctgtccctc	
atctcgctg tctctgggtga ctccatcagc agtggtaact	120
ggtgaatctg ggtccgcag	
ccccccagggaa agggggctggaa gtggatttggg gaaatccatc	180
atagtgggag cacctactac	
aacccgtccc tcaagagtcg aatcaccatg tccgttagaca	240
cgtccaagaa ccagttctac	
ctgaagctga gctctgtgac cgccgcggac acggccgtgt	296
attactgtgc gagata	

<210> SEQ ID NO 500

<211> LENGTH: 296

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 500

caggtgcagc tgcaggagtc gggcccagga ctggtaa	60
cttcggagac cctgtccctc	
atctcgctg tctctgggtga ctccatcagc agtggtaact	120
ggtgaatctg ggtccgcag	
ccccccagggaa agggggctggaa gtggatttggg gaaatccatc	180
atagtgggag cacctactac	
aacccgtccc tcaagagtcg aatcaccatg tccgttagaca	240
cgtccaagaa ccagttctac	
ctgaagctga gctctgtgac cgccgcggac acggccgtgt	296
attactgtgc gagata	

<210> SEQ ID NO 501

<211> LENGTH: 287

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 501

caggtgcagc tgcaggagtc gggcccagga ctggtaa	60
cttcggagac cctgtccctc	
atctcgctg tctctgggtga ctccatcagc agtggtaact	120
ggtgaatctg ggtccgcag	
ccccccagggaa agggggctggaa gtggatttggg gaaatccatc	180
atagtgggag cacctactac	
aacccgtccc tcaagagtcg aatcaccatg tccgttagaca	240
cgtccaagaa ccagttctcc	
ctgaagctga gctctgtgac cgccgcggac acggccgtgt	287
attactgtgc	

<210> SEQ ID NO 502

<211> LENGTH: 287

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 502

caggtgcagc tgcaggagtc gggcccagga ctggtaa	60
cttcggagac cctgtccctc	
atctcgctg tctctgggtga ctccatcagc agtggtaact	120
ggtgaatctg ggtccgcag	

-continued

ccccccaggga aggggcttggaa gtggattttgggg gaaaatccatc atagtggggag cacctactac	180
aacccgtccc tcaagagtcg aatcaccatg tccgttagaca cgtccaagaa ccagttctac	240
ctgaagctga gctctgtgac cgccgcggac acggccgtgt attactg	287

<210> SEQ ID NO 503
<211> LENGTH: 287
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 503

caggtgcagc tgcaggagtc gggccaggaa ctgggtgaagc ttccggagac cctgtccctc	60
atctgctgtg tctctggta ctccatcagc agtggtaact ggtgaatctg ggtccgcag	120
ccccccaggga aggggcttggaa gtggattttgggg gaaaatccatc atagtggggag cacctactac	180
aacccgtccc tcaagagtcg aatcaccatg tccgttagaca cgtccaagaa ccagttctac	240
ctgaagctga gctctgtgac cgccgcggac acggccgtgt attactg	287

<210> SEQ ID NO 504
<211> LENGTH: 287
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 504

caggtgcagc tgcaggagtc gggccaggaa ctgggtgaagc ttccggagac cctgtccctc	60
atctgctgtg tctctggta ctccatcagc agtggtaact ggtgaatctg ggtccgcag	120
ccccccaggga aggggcttggaa gtggattttgggg gaaaatccatc atagtggggag cacctactac	180
aacccgtccc tcaagagtcg aatcaccatg tccgttagaca cgtccaagaa ccagttctac	240
ctgaagctga gctctgtgac cgccgcggac acggccgtgt attactg	287

<210> SEQ ID NO 505
<211> LENGTH: 286
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 505

caggtgcagc tgcaggagtc gggccaggaa ctgggtgaagc ttccggagac cctgtccctc	60
atctgctgtg tctctggta ctccatcagc agtggtaact ggtgaatctg ggtccgcag	120
ccccccaggga aggggcttggaa gtggattttgggg gaaaatccatc atagtggggag cacctactac	180
aacccgtccc tcaagagtcg aatcaccatg tccgttagaca cgtccaaggaa ccagttctcc	240
ctgaagctga gctctgtgac cgccgcagac acggccgtgt attact	286

<210> SEQ ID NO 506
<211> LENGTH: 296
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 506

caggtgcagc tgcaggagtc gggccaggaa ctgggtgaagc ttccggagac cctgtccctc	60
atctgctgtg tctctggta ctccatcagc agtggtaact ggtgaatctg ggtccgcag	120
ccccccaggga aggggcttggaa gtggattttgggg gaaaatccatc atagtggggag cacctactac	180
aacccgtccc tcaagagtcg aatcaccatg tccgttagaca cgtccaagaa ccagttctac	240
ctgaagctga gctctgtgac cgccgcggac acggccgtgt attactgtc gagaga	296

-continued

<210> SEQ ID NO 507
<211> LENGTH: 296
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 507

caggtgcagc tgcaggagtc gggcccagga ctggtaa	60
cttcggagac cctgtccctc	
atctctggta ctccatcagc agtggtaact ggtgaatctg	120
ggtccgcag	
ccccccaggaa aggggctgga gtggattggg gaaatccatc atagtgggag cacctactac	180
aaccctgtccc tcaagatcg aatcaccatg tccgttagaca cgtccaagaa ccagttctcc	240
ctgaagctga gctctgtgac cgccgtggac acggccgtgt attactgtgc gagaaa	296

<210> SEQ ID NO 508
<211> LENGTH: 293
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 508

caggtgcagc tgcaggagtc gggcccagga ctggtaa	60
cttcggagac cctgtccctc	
acctgcactg tctctggtg ctccatcagt agttactact ggagctggat ccggcagccc	120
ccagggaaagg gactggagtg gattgggtat atctattaca gtgggagcac caactacaac	180
ccctccctca agagtcgagt caccatatca gtagacacgt ccaagaacca gttctccctg	240
aagctgagct ctgtgaccgc tgccggacacg gccgtgtatt actgtgcgag aga	293

<210> SEQ ID NO 509
<211> LENGTH: 293
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 509

caggtgcagc tgcaggagtc gggcccagga ctggtaa	60
cttcggagac cctgtccctc	
acctgcactg tctctggtg ctccgtcagt agttactact ggagctggat ccggcagccc	120
ccagggaaagg gactggagtg gattgggtat atctattaca gtgggagcac caactacaac	180
ccctccctca agagtcgagt caccatatca gtagacacgt ccaagaacca gttctccctg	240
aagctgagct ctgtgaccgc tgccggacacg gccgtgtatt actgtgcgag aga	293

<210> SEQ ID NO 510
<211> LENGTH: 288
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 510

caggtgcagc tgcaggagtc gggcccagga ctggtaa	60
cttcggagac cctgtccctc	
acctgcactg tctctggtg ctccatcagt agttactact ggagctggat ccggcagccc	120
ccagggaaagg gactggagtg gattgggtat atctattaca gtgggagcac caactacaac	180
ccctccctca agagtcgagt caccatatca gtagacacgt ccaagaacca attctccctg	240
aagctgagct ctgtgaccgc tgccggacacg gccgtgtatt actgtgcg	288

<210> SEQ ID NO 511
<211> LENGTH: 288
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 511

-continued

caggtgcagc tgcaggagtc gggcccgagga ctggtaaagc cttcgagac cctgtccctc	60
acctgcactg tctctggtgg ctccatcagt agttactact ggagctggat ccggcagccc	120
ccagggaaagg gactggagtg gattgggtat atctattata gtgggagcac ctactacaac	180
ccgtccctca agagtcgagt caccatgtca gtagacacgt ccaagaacca gttctccctg	240
aagctgagct ctgtgaccgc cgccagacacg gctgtgtatt actgtgcg	288

<210> SEQ ID NO 512

<211> LENGTH: 288

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 512

caggtgcagc tgcaggagtc gggcccgagga ctggtaaagc cttcgagac cctgtccctc	60
acctgcactg tctctggtgg ctccatcagt agttactact ggagctggat ccggcagccc	120
ccggggaaagg gactggagtg gattgggtat atctattata gtgggagcac ctactacaac	180
ccgtccctca agagtcgagt caccatatcc gtagacacgt ccaagaacca gttctccctg	240
aagctgagct ctgtgaccgc cgccagacacg gctgtgtatt actgtgcg	288

<210> SEQ ID NO 513

<211> LENGTH: 288

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 513

caggtgcagc tgcaggagtc gggcccgagga ctggtaaagc cttcgagac cctgtccctc	60
acctgcactg tcactggtgg ctccatcagt agttactact ggagctggat ccggcagccc	120
gtctggaaagg gcctggagtg gattgggtac atctattaca gtgggagcac ctactacaac	180
ccgtccctca agagtcgagt taccatatca gtagacacgt ctaagaacca gttctccctg	240
aagctgagct ctgtgactgc cgccggacacg gccgtgtatt actgtgcg	288

<210> SEQ ID NO 514

<211> LENGTH: 291

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 514

caggtgcagc tgcaggagtc gggcccgagga ctggtaaagc cttcgacac cctgtccctc	60
acctgcactg tctctggtgg ctccatcagt agttactact ggagctggat ccggcagccc	120
ccagggaaagg gactggagtg gattgggtat atctattaca gtgggagcac caactacaac	180
ccgtccctca agagtcgagt caccatatca gtagacacgt ccaagaacca gttctccctg	240
aagctgagct ctgtgaccgc tgccggacacg gccgtgtatt actgtgcgag a	291

<210> SEQ ID NO 515

<211> LENGTH: 237

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<220> FEATURE:

<221> NAME/KEY: modified_base

<222> LOCATION: (36)..(36)

<223> OTHER INFORMATION: a, c, t or g

<220> FEATURE:

<221> NAME/KEY: modified_base

<222> LOCATION: (214)..(214)

<223> OTHER INFORMATION: a, c, t or g

-continued

<400> SEQUENCE: 515

tccctcacct	gcactgtctc	tggggctcc	atcagnagtt	actactggag	ctggatccgg	60
cagccccca	ggaagggact	ggagtggatt	gggtatatct	attacagtgg	gagcaccaac	120
tacaaccct	ccctaagag	tcgagtcacc	atatcagtag	acacgtccaa	gaaccaggta	180
tccctgaagc	tgagctctgt	gaccgcccga	gacncggccg	tgtattactg	tgcgaga	237

<210> SEQ ID NO 516

<211> LENGTH: 221

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<220> FEATURE:	
<221> NAME/KEY: modified_base	
<222> LOCATION: (54)..(54)	
<223> OTHER INFORMATION: a, c, t or g	
<220> FEATURE:	
<221> NAME/KEY: modified_base	
<222> LOCATION: (56)..(58)	
<223> OTHER INFORMATION: a, c, t or g	

<400> SEQUENCE: 516

tctgggtggct	ccatcagtag	ttactactgg	agctggatcc	ggcagcccc	aggnannnga	60
ctggagtgg	ttgggtata	ctattacagt	gggagcacca	actacaaccc	ctccctcaag	120
agtcgagtca	ccatatcagt	agacacgtcc	aagaaccagt	tctccctgaa	gctgagctct	180
gtgaccgctg	cggacacggc	cgtgtattac	tgtgcgagag	g		221

<210> SEQ ID NO 517

<211> LENGTH: 293

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 517

caggtgcagc	taacgcgtg	gggcgcagga	ctgttgaagc	cttcggagac	cctgtccctc	60
acctgcgtcg	tctatggtgg	ctccatcagt	agttactact	ggagctggat	ccggcagccc	120
gccgggaagg	ggctggagtg	gattggcggt	atctatacca	gtgggagcac	caactacaac	180
ccctccctca	agagtcgagt	caccatgtca	gtagacacgt	ccaagaacca	gttctccctg	240
aagctgagct	ctgtgaccgc	cgcggacacg	gccgtgtatt	actgtgcgag	ata	293

<210> SEQ ID NO 518

<211> LENGTH: 299

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 518

caggtgcagc	tgcaggagtc	gggcccagga	ctgggtgaagc	cttcggagac	cctgtccctc	60
acctgcactg	tctctggtgg	ctccgtcagc	agtggtagtt	actactggag	ctggatccgg	120
cagccccca	ggaagggact	ggagtggatt	gggtatatct	attacagtgg	gagcaccaac	180
tacaaccct	ccctaagag	tcgagtcacc	atatcagtag	acacgtccaa	gaaccaggta	240
tccctgaagc	tgagctctgt	gaccgctg	gacacggccg	tgtattactg	tgcgagaga	299

<210> SEQ ID NO 519

<211> LENGTH: 299

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 519

caggtgcagc	tgcaggagtc	gggcccagga	ctgggtgaagc	cttcacagac	cctgtccctc	60
------------	------------	------------	-------------	------------	------------	----

-continued

```
acctgcactg tctctggtgg ctccatcagc agtggtagtt actactggag ctggatccgg      120
```

```
cagccccccg ggaagggact ggagtggatt gggcttatct ataccagtgg gagcaccaac      180
```

```
tacaaccctt ccctcaagag tcgagtcacc atatcagtag acacgtccaa gaaccagttc      240
```

```
tccctgaagc tgagctctgt gaccgcccga gacacggccg tgtattactg tgcgagaga      299
```

<210> SEQ ID NO 520

<211> LENGTH: 299

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 520

```
caggtgcagc tgcaggagtc gggcccgagga ctgggtgaagc cttcggagac cctgtccctc      60
```

```
acctgcactg tctctggtgg ctccgtcagc agtggtagtt actactggag ctggatccgg      120
```

```
cagccccccag ggaagggact ggagtggatt gggtatatct attacagtgg gagcaccaac      180
```

```
tacaaccctt ccctcaagag tcgagtcacc atatcagtag acacgtccaa gaaccacttc      240
```

```
tccctgaagc tgagctctgt gaccgctgac gacacggccg tgtattactg tgcgagaga      299
```

<210> SEQ ID NO 521

<211> LENGTH: 287

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 521

```
caggtgcagc tgcaggagtc gggcccgagga ctgggtgaagc cttcggagac cctgtccctc      60
```

```
acctgcactg tctctggtgg ctccgtcagc agtggtagtt actactggag ctggatccgg      120
```

```
cagccccccag ggaagggact ggagtggatt gggtatatct attacagtgg gagcaccaac      180
```

```
tacaaccctt ccctcaagag tcgagtcacc atatcagtag acacgtccaa gaaccagttc      240
```

```
tccctgaagc tgagctctgt gaccgctgac acggccgtgt attactg                      287
```

<210> SEQ ID NO 522

<211> LENGTH: 297

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 522

```
cagctgcagc tgcaggagtc gggcccgagga ctgggtgaagc cttcggagac cctgtccctc      60
```

```
acctgcactg tctctggtgg ctccatcagc agtggtagtt actactgggg ctggatccgg      120
```

```
cagccccccag ggaagggact ggagtggatt gggtatatct attacagtgg gagcaccaac      180
```

```
tacaaccctt ccctcaagag tcgagtcacc atatcagtag acaagtccaa gaaccagttc      240
```

```
tccctgaagc tgagctctgt gaccgcccgcg gacacggccg tgtattactg tgcgagaga      297
```

<210> SEQ ID NO 523

<211> LENGTH: 227

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 523

```
tctggggct ccgtcagcag tggtagttac tactggagct ggatccggca gccccccaggg      60
```

```
aaggggactgg agtggattgg gtatatctat tacagtggga gcaccaacta caaccctcc      120
```

```
ctcaagagtc gagtcaccat atcagtagac acgtccaaga accagttctc cctgaagctg      180
```

```
agctctgtga ccggccggca cacggccgtg tattactgtg ccagaga                      227
```

-continued

<210> SEQ ID NO 524
<211> LENGTH: 227
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 524

tctggtgct ccgtcagcag tggtagttac tactggagct ggatccggca gcccccaagg	60
aaggggactgg agtggattgg gtatatctat tacagtggga gcaccaacta caaccctcc	120
ctcaagagtc gagtcaccat atcagtagac acgtccaaga accagttctc cctgaagctg	180
agctctgtga ccgctgcgga cacggccgtg tattactgtg cgagaca	227

<210> SEQ ID NO 525
<211> LENGTH: 299
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 525

caggtgcagc tgcaggagtc gggcccagga ctggtaagc cttcgagac cctgtccctc	60
acctgcactg tctctgggtt ctccgtcagc agtgggttgtt actactggag ctggatccgg	120
cagcccccaag ggaaggggact ggagtggatt gggtatatctt attacagtgg gagcaccaac	180
tacaaccctt ccctcaagag tcgagtcacc atatcagtag acacgtccaa gaaccagg	240
tccctgaagc tgagctctgt gaccgctgcg gacacggccg tgtattactg tgcgagaga	299

<210> SEQ ID NO 526
<211> LENGTH: 294
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 526

caggtgcagc tgcaggagtc gggcccagga ctggtaagc cttcgagac cctgtccctc	60
acctgcgtcg tctctgggtt ctccatcagc agtggttactt actggggctg gatccggcag	120
ccccccagggaa agggggctgaa gtggattttttt agtatctatc atagtgggag cacctactac	180
aaccctgtccc tcaagagtcg agtcaccata tcagtagaca cgtccaagaa ccagttctcc	240
ctgaagctga gctctgtgac cgccgcagac acggccgtgtt attactgtgc gaga	294

<210> SEQ ID NO 527
<211> LENGTH: 294
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 527

caggtgcagc tgcaggagtc gggcccagga ctggtaagc cttcgagac cctgtccctc	60
acctgcactg tctctgggtt ctccatcagc agtggttactt actggggctg gatccggcag	120
ccccccagggaa agggggctgaa gtggattttttt agtatctatc atagtgggag cacctactac	180
aaccctgtccc tcaagagtcg agtcaccata tcagtagaca cgtccaagaa ccagttctcc	240
ctgaagctga gctctgtgac cgccgcagac acggccgtgtt attactgtgc gaga	294

<210> SEQ ID NO 528
<211> LENGTH: 296
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 528

caggtgcagc tgcaggagtc gggcccagga ctggtaagc cttcgagac cctgtccctc	60
---	----

-continued

acctgcgttg tctctggtgg ctccatcagc agtagtaact ggtggagctg ggtccgcccag	120
cccccaggaa agggggcttgg a gttggattttggaa aataatctatc atagtgggaa ccccaactac	180
aacccgtccc tcaagagtcg agtcaccata tcaatagaca agtccaagaa ccaattctcc	240
ctgaagctga gctctgtgac cgccgcggac acggccgtgtt attactgtgc gagaga	296

<210> SEQ ID NO 529

<211> LENGTH: 296

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 529

gagggtgcagc tgggtgcagtc tggagcagag gtgaaaaagc cggggggagtc tctgaagatc	60
tccctgttaagg gttctggata cagctttacc agctactggaa tcggctgggt gcgccagatg	120
cccgaaaag gcctggagtg gatggggatc atctatcctg gtgactctga taccagatac	180
agcccgctct tccaaaggcca ggtcaccatc tcagccgaca agtccatcag caccgcctac	240
ctgcagtggaa gcagcctgaa ggcctcgac accgcccattgtt attactgtgc gagaca	296

<210> SEQ ID NO 530

<211> LENGTH: 296

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 530

gagggtgcagc tgggtgcagtc tggagcagag gtgaaaaagc cggggggagtc tctgaagatc	60
tccctgttaagg gttctggata cagctttacc agctactggaa tcggctgggt gcgccagatg	120
cccgaaaag gcctggagtg gatggggatc atctatcctg gtgactctga taccagatac	180
agcccgctct tccaaaggcca ggtcaccatc tcagccgaca agtccatcag caccgcctac	240
ctgcagtggaa gcagcctgaa ggcctcgac accgcccattgtt attactgtgc gagaca	296

<210> SEQ ID NO 531

<211> LENGTH: 294

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 531

gagggtgcagc tgggtgcagtc tggagcagag gtgaaaaagc cggggggagtc tctgaagatc	60
tccctgttaagg gttctggata cagctttacc agctactggaa tcggctgggt gcgccagatg	120
cccgaaaag gcctggagtg gatggggatc atctatcctg gtgactctga taccagatac	180
agcccgctct tccaaaggcca ggtcaccatc tcagccgaca agtccatcag caccgcctac	240
ctgcagtggaa gcagcctgaa ggcctcgac accgcccattgtt attactgtgc gaga	294

<210> SEQ ID NO 532

<211> LENGTH: 294

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 532

gagggtgcagc tgggtgcagtc tggagcagag gtgaaaaagc cggggggagtc tctgaagatc	60
tccctgttaagg gttctggata cagctttacc agctactggaa tcggctgggt gcgccagatg	120
cccgaaaag gcctggagtg gatggggatc atctatcctg gtgactctga taccagatac	180
agcccgctct tccaaaggcca ggtcaccatc tcagccgaca agcccatcag caccgcctac	240

-continued

ctgcagtgga gcagecctgaa ggcctcgac accgcccatttgtt attactgtgc gaga 294

<210> SEQ ID NO 533
<211> LENGTH: 245
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 533

aaaageccgg ggagtctctg aagatctctt gtaagggttc tggatacagc tttaccagct	60
actggatcggtt ctgggtgcgc cagatgcaca ggaaaggcct ggagtgatg gggatcatct	120
atcctggatgtt ctctgatacc agatacagcc cgtccttcca aggccaggctt accatctcag	180
ccgacaagtc catcagcacc gcctacctgc agtggagcag cctgaaggcc tcggacaccg	240
ccatgtt	245

<210> SEQ ID NO 534
<211> LENGTH: 294
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 534

gaggtgcagc tggtgcagtc tgcagcagag gtgaaaagac ccggggagtc tctgaggatc	60
tccctgtttaa cttctggata cagctttacc agctactgga tccactgggt gcgccagatg	120
cccgaaaaag aactggagtg gatggggagg atctatcctg ggaactctga taccagatac	180
agcccatctt tccaaggccca cgtcaccatc tcagccgaca gctccagcag caccgcctac	240
ctgcagtgga gcagecctgaa ggcctcgac accgcccatttgtt attactgtgc gaga	294

<210> SEQ ID NO 535
<211> LENGTH: 294
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 535

gaagtgcagc tggtgcagtc tggagcagag gtgaaaagc ccggggagtc tctgaggatc	60
tccctgtttaa cttctggata cagctttacc agctactgga tccactgggt gcgccagatg	120
cccgaaaaag gcttggagtg gatggggagg atctatcctg gtaactctta taccatcac	180
agcccatctt tccaaggccca cgtcaccatc tcagctgaca agtccatcag cactgcctac	240
ctgcagtgga gcagecctgaa ggcctcgac accgcccatttgtt attactgtgc gaga	294

<210> SEQ ID NO 536
<211> LENGTH: 295
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 536

gaagtgcagc tggtgcagtc tggagcagag gtgaaaagc ccggggagtc tctgaggatc	60
tccctgtttaa cttctggata cagctttacc agctactgga tccactgggt gcgccagatg	120
cccgaaaaag gcttggagtg gatggggagg atctatcctg gtaactctta taccatcac	180
agcccatctt tccaaggccca cgtcaccatc tcagctgaca agtccatcag cactgcctac	240
ctgcagtgga gcagecctgaa ggcctcgac accgcccatttgtt attactgtgc gaga	295

<210> SEQ ID NO 537
<211> LENGTH: 294
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

-continued

<400> SEQUENCE: 537

gaagtgcagc tgggtgcagtc cggagcagag gtaaaaaggc cgggggagtc tctgaggatc	60
tccctgttaagg gttctggata cagctttacc agctactgga tcagctgggt gcgccagatg	120
cccgaaaag gcctggagtg gatggggagg attgatccta gtgacttta taccaactac	180
agcccgctct tccaaggcca cgtcaccatc tcagctgaca agtccatcag cactgcctac	240
ctgcagtggaa gcagcgtgaa ggcctcgac accgcatgt attactgtgc gaga	294

<210> SEQ ID NO 538

<211> LENGTH: 294
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 538

gaagtgcagc tgggtgcagtc tggagcagag gtaaaaaggc cgggggagtc tctgaggatc	60
tccctgttaagg gttctggata cagctttacc agctactgga tcagctgggt gcgccagatg	120
cccgaaaag gcctggagtg gatggggagg attgatccta gtgacttta taccaactac	180
agcccgctct tccaaggcca ggtcaccatc tcagctgaca agtccatcag cactgcctac	240
ctgcagtggaa gcagcgtgaa ggcctcgac accgcatgt attactgtgc gaga	294

<210> SEQ ID NO 539

<211> LENGTH: 305
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 539

cagggtacagc tgccagcagtc aggtccagga ctgggtgaagc cctcgcagac cctctcactc	60
acctgtgccca tctccgggaa cagtgtctct agcaacagtgc tgcttgaa ctggatcagg	120
cagtccccat cgagaggcct tgagtggctg ggaaggacat actacaggc caagtggtat	180
aatgattatg cagtatctgt gaaaagtgcata ataaccatca acccagacac atccaagaac	240
cagttctccc tgccagctgaa ctctgtgact cccgaggaca cggctgtgta ttactgtgca	300
agaga	305

<210> SEQ ID NO 540

<211> LENGTH: 305
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 540

cagggtacagc tgccagcagtc aggtccggaa ctgggtgaagc cctcgcagac cctctcactc	60
acctgtgccca tctccgggaa cagtgtctct agcaacagtgc tgcttgaa ctggatcagg	120
cagtccccat cgagaggcct tgagtggctg ggaaggacat actacaggc caagtggtat	180
aatgattatg cagtatctgt gaaaagtgcata ataaccatca acccagacac atccaagaac	240
cagttctccc tgccagctgaa ctctgtgact cccgaggaca cggctgtgta ttactgtgca	300
agaga	305

<210> SEQ ID NO 541

<211> LENGTH: 294
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 541

-continued

caggtgcagc tggtaatac tgggtcttag ttgaagaagc ctggggcctc agtgaaggtt	60
tcctgcaagg cttctggata cacccact agctatgcta tgaattgggt gcgacaggcc	120
cctggacaag ggcttgagtg gatggatgg atcaacacca acactggaa cccaacgtat	180
gcccaggcgt tcacaggacg gtttgttcc tccttggaca cctctgtcag cacggcatat	240
ctgcagatct gcacgctaaa ggctgaggac actgcccgtt attactgtgc gagaga	294
<210> SEQ ID NO 542	
<211> LENGTH: 296	
<212> TYPE: DNA	
<213> ORGANISM: Homo sapiens	
<400> SEQUENCE: 542	
caggtgcagc tggtaatac tgggtcttag ttgaagaagc ctggggcctc agtgaaggtt	60
tcctgcaagg cttctggata cacccact agctatgcta tgaattgggt gcgacaggcc	120
cctggacaag ggcttgagtg gatggatgg atcaacacca acactggaa cccaacgtat	180
gcccaggcgt tcacaggacg gtttgttcc tccttggaca cctctgtcag cacggcatat	240
ctgcagatct gcacgctaaa ggctgaggac actgcccgtt attactgtgc gagaga	296
<210> SEQ ID NO 543	
<211> LENGTH: 274	
<212> TYPE: DNA	
<213> ORGANISM: Homo sapiens	
<400> SEQUENCE: 543	
caggtgcagc tggtaatac tgggtcttag ttgaagaagc ctggggcctc agtgaaggtt	60
tcctgcaagg cttctggata cacccact agctatgcta tgaattgggt gcgacaggcc	120
cctggacaag ggcttgagtg gatggatgg atcaacacca acactggaa cccaacgtat	180
gcccaggcgt tcacaggacg gtttgttcc tccttggaca cctctgtcag cacggcatat	240
ctgcagatct gcacgctaaa ggctgaggac actg	274
<210> SEQ ID NO 544	
<211> LENGTH: 289	
<212> TYPE: DNA	
<213> ORGANISM: Homo sapiens	
<400> SEQUENCE: 544	
ctgcagctgg tgcagtctgg gcctgagggt aagaagcctg gggcctcact gaaggcttcc	60
tataagtctt ctggttacac cttcaccatc tatggatgtatg ataggatgtatg atagaccctt	120
ggacaggcgt ttgagtgat gtgtatggatc atcacctaca ctggaaaccc aacgtataacc	180
cacggcttca caggatggtt tgcgttccatc atggacacgt ctgtcagcac ggcgtgttcc	240
cagatcagca gcctaaaggc tgaggacacg gcccgttattt actgtgcgaa	289
<210> SEQ ID NO 545	
<211> LENGTH: 296	
<212> TYPE: DNA	
<213> ORGANISM: Homo sapiens	
<400> SEQUENCE: 545	
caggtgcagc tggtaatac tgggtcttag gtgaaggcgc ctggggcctc agtgaaggcc	60
tcctgcaagg cttctggata cacccact acctatggta tgaattgggt gcgacaggcc	120
cctggacaag ggcttgagtg gatggatgg ttcaacaccc acactggaa cccaacatat	180
gcccaggcgt tcacaggacg gtttgttcc tccatggaca cctctgtcag cacggcatat	240

-continued

ctgcagatca gcagcctaaa ggctgaggac atggccatgt attactgtgc gagata 296

<210> SEQ ID NO 546
<211> LENGTH: 26
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TCR gamma primer

<400> SEQUENCE: 546

ggaggggaag gccccacagt gtcttc 26

<210> SEQ ID NO 547
<211> LENGTH: 28
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TCR gamma primer

<400> SEQUENCE: 547

ccaaatcagg ctttggagca cctgatct 28

<210> SEQ ID NO 548
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TCR gamma primer

<400> SEQUENCE: 548

caaaggctta gaatatttat tacatgt 27

<210> SEQ ID NO 549
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TCR gamma primer

<400> SEQUENCE: 549

tgaagtcatca cagttcctgg tgtccat 27

<210> SEQ ID NO 550
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: a, c, t or g

<400> SEQUENCE: 550

-continued

tgggtgcac aggccctgg acaaggcctt gagtgg 36

```

<210> SEQ_ID NO 551
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 551

```

tgggtgcac aggctcctgg aaaaggcctt gagtgg 36

```

<210> SEQ_ID NO 552
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 552

```

tgggtgcgcc aggcccccg acaaaggcctt gagtgg 36

```

<210> SEQ_ID NO 553
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 553

```

tgggtgcac aggcccccg acaagcgctt gagtgg 36

```

<210> SEQ_ID NO 554
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 554

```

tgggtgcac aggccccag acaagcgctt gagtgg 36

```

<210> SEQ_ID NO 555
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 555

```

tgggtgcac aggctcggtgg acaacgcctt gagtgg 36

-continued

```

<210> SEQ_ID NO 556
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 556

```

tggttgcaac aggccctgg acaaggcgtt gaaagg

36

```

<210> SEQ_ID NO 557
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 557

```

tgggtgcgac aggccactgg acaaggcgtt gagtggtt

36

```

<210> SEQ_ID NO 558
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 558

```

tgggtgcaac agtccctgg acaaggcgtt gagtggtt

36

```

<210> SEQ_ID NO 559
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 559

```

tgggtgcaac aggccctgg aaaaggcgtt gagtggtt

36

```

<210> SEQ_ID NO 560
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (31)..(31)
<223> OTHER INFORMATION: a, c, t or g

<400> SEQUENCE: 560

```

tgggtgtgac aaagccctgg acaaggcgtt nagtggtt

36

-continued

```

<210> SEQ ID NO 561
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 561

```

tgggtgcgac aggccctgg acaagagctt gggtgg 36

```

<210> SEQ ID NO 562
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 562

```

tgggtgtgac aggccctga acaaggcctt gagtgg 36

```

<210> SEQ ID NO 563
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 563

```

tggatgcgcc aggccctgg acaaaggctt gagtgg 36

```

<210> SEQ ID NO 564
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 564

```

tggatgcgcc aggccctgg acaaggcttc gagtgg 36

```

<210> SEQ ID NO 565
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 565

```

tgggtgtgac aggccctgg acaaggactt gagtgg 36

```

<210> SEQ ID NO 566
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence

```

-continued

<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 566

tgggtgcacc aggtccatgc acaaggcctt gagtgg

36

<210> SEQ ID NO 567
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 567

tgggtgcgcc aggtccatgc acaaggcctt gagtgg

36

<210> SEQ ID NO 568
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 568

tgggtgtgcc aggtccatgc acaaggcctt gagtgg

36

<210> SEQ ID NO 569
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 569

tagatctgtc agccctcagc aaaggccctg gagtgg

36

<210> SEQ ID NO 570
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 570

tggatccgtc agccccagg gaaggccctg gagtgg

36

<210> SEQ ID NO 571
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
primer
<220> FEATURE:

-continued

<223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 571

tggatccgtc agccccagg aaaggccctg gagtgg

36

<210> SEQ ID NO 572

<211> LENGTH: 36

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<220> FEATURE:

<223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 572

tggatccgtc agccccggg gaaggccctg gagtgg

36

<210> SEQ ID NO 573

<211> LENGTH: 36

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<220> FEATURE:

<223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 573

tgggtccgcc aggctccagg gaaaaggctg gagtgg

36

<210> SEQ ID NO 574

<211> LENGTH: 36

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<220> FEATURE:

<223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 574

tgggtccggc aagctccagg gaaggccctg gagtgg

36

<210> SEQ ID NO 575

<211> LENGTH: 36

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<220> FEATURE:

<223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 575

tggatccgcc aggctccagg gaaggccctg gagtgg

36

<210> SEQ ID NO 576

<211> LENGTH: 36

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<220> FEATURE:

<223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 576

-continued

tgggtccgcc aagctacagg aaaaggtctg gagtgg

36

```

<210> SEQ ID NO 577
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 577

```

tgggtccgcc aggctccagg gaaggggctg gagtgg

36

```

<210> SEQ ID NO 578
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 578

```

tgggccccca aggctccagg aaaggggctg gagtgg

36

```

<210> SEQ ID NO 579
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 579

```

tgggtccgcc aggctccagg aaaggggctg gagtgg

36

```

<210> SEQ ID NO 580
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 580

```

tgggtccgcc aagctccagg gaaggggctg gagtgg

36

```

<210> SEQ ID NO 581
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 581

```

gggggtccgcc aggctccgg gaaggggctg gaatgg

36

<210> SEQ ID NO 582

-continued

```

<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 582

```

tgtgtccgcc aggctccagg gaatgggctg gagttg 36

```

<210> SEQ ID NO 583
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 583

```

tgggtccgcc aggctccagg caaggggcta gagtgg 36

```

<210> SEQ ID NO 584
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 584

```

tgggtccgcc aggctccagg caaggggctg gagtgg 36

```

<210> SEQ ID NO 585
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 585

```

tgggtccgcc aggccccagg caaggggcta gagtgg 36

```

<210> SEQ ID NO 586
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 586

```

tgggtccgcc aggctccggg caaggggcta gagtgg 36

```

<210> SEQ ID NO 587
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

```

-continued

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer
<400> SEQUENCE: 587

cgagttcacc agtctccagg caaggggctg gagtga

36

<210> SEQ ID NO 588
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer
<400> SEQUENCE: 588

tgggtccatc aggctccagg aaaggggctg gagtgg

36

<210> SEQ ID NO 589
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer
<400> SEQUENCE: 589

tgggtccgtc aagctccggg gaagggtctg gagtgg

36

<210> SEQ ID NO 590
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer
<400> SEQUENCE: 590

tgggtccgtc aagctccagg gaagggtctg gagtgg

36

<210> SEQ ID NO 591
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer
<400> SEQUENCE: 591

tgggttcgcc gggctccagg gaagggtctg gagtgg

36

<210> SEQ ID NO 592
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer

-continued

<400> SEQUENCE: 592

tgggttcgcc gggctccagg gaagggtccg gagtgg

36

<210> SEQ ID NO 593
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 593

tggttccgcc aggctccagg gaaggggctg gagtgg

36

<210> SEQ ID NO 594
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 594

tgggtctgcc aggctccgga gaaggggctg gagtgg

36

<210> SEQ ID NO 595
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 595

tgggtctgcc aggctccgga gaaggggcag gagtgg

36

<210> SEQ ID NO 596
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 596

tgggtccgcc agcctccagg gaaggggctg gagtgg

36

<210> SEQ ID NO 597
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 597

tcagattccc aagctccagg gaaggggctg gagtga

36

-continued

<210> SEQ ID NO 598
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 598

tcagattccc aggctccagg gaaggggctg gagtga

36

<210> SEQ ID NO 599
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 599

tgggtccgcc aggctccaaag aaagggtttg tagtgg

36

<210> SEQ ID NO 600
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 600

tgggtcaatg agactctagg gaaggggctg gaggga

36

<210> SEQ ID NO 601
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 601

tgggtccgcc aggctccagg gaaggactg gaatat

36

<210> SEQ ID NO 602
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 602

tgggtccgcc aggctccagg gaaggggctg gagtgg

36

<210> SEQ ID NO 603
<211> LENGTH: 36

-continued

<212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
 <220> FEATURE:
 <223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 603

tgggtccgcc aggctccgg gaaaaggctg gagtgg

36

<210> SEQ ID NO 604
 <211> LENGTH: 36
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
 <220> FEATURE:
 <223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 604

tgggtccgcc aagctccagg gaaggggctg gtgtgg

36

<210> SEQ ID NO 605
 <211> LENGTH: 36
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
 <220> FEATURE:
 <223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 605

tgggtccgcc aggctccagg gaagggctg gagtgg

36

<210> SEQ ID NO 606
 <211> LENGTH: 36
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
 <220> FEATURE:
 <223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 606

tgggtccgcc aggctcaagg gaaaaggcta gagttg

36

<210> SEQ ID NO 607
 <211> LENGTH: 36
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
 <220> FEATURE:
 <223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 607

tgggtccgcc aggctccagg gaagggactg gagtgg

36

<210> SEQ ID NO 608
 <211> LENGTH: 36
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic

-continued

```

primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 608

tgggttcgcc aggctccagg aaaaggtctg gagtgg                                36

<210> SEQ ID NO 609
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 609

tggatccacc aggctccagg gaagggtctg gagtgg                                36

<210> SEQ ID NO 610
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 610

tgggtccgcc aatctccagg gaaggggctg gtgtga                                36

<210> SEQ ID NO 611
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 611

tgggtctctt aggctccagg aaaggggctg gagtgg                                36

<210> SEQ ID NO 612
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 612

tggatccggc agcccccagg gaagggactg gagtgg                                36

<210> SEQ ID NO 613
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer

```

-continued

<400> SEQUENCE: 613

tggatccggc agccaccagg gaagggcctg gagtgg

36

<210> SEQ ID NO 614
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 614

tggatccgcc agccccagg gaagggcctg gagtgg

36

<210> SEQ ID NO 615
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (14)..(14)
<223> OTHER INFORMATION: a, c, t or g

<400> SEQUENCE: 615

tggatccgcc agcncccagg gaagggcctg gagtgg

36

<210> SEQ ID NO 616
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 616

tggatccgcc agcacccagg gaagggcctg gagtgg

36

<210> SEQ ID NO 617
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 617

tggatccgcc agccccagg gaaggggctg gagtgg

36

<210> SEQ ID NO 618
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer

-continued

<400> SEQUENCE: 618

tggatccgcc agccccctagg gaaggggctg gagtgg

36

<210> SEQ ID NO 619
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 619

tggatccgcc agcccccagg gaagggactg gagtgg

36

<210> SEQ ID NO 620
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 620

tggatccggc agcccccagg gaaggggctg gagtgg

36

<210> SEQ ID NO 621
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 621

tggatccggc agcccccagg gaaggggctg gagtgg

36

<210> SEQ ID NO 622
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 622

tggatccggc agccgcggg gaagggactg gagtgg

36

<210> SEQ ID NO 623
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 623

tggatccggc agccgcggg gaagggactg gagtgg

36

-continued

<210> SEQ ID NO 624
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 624

tggatccggc agcccgctgg gaagggcctg gagtgg

36

<210> SEQ ID NO 625
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 625

tggatccggc agcccgccgg gaaggggctg gagtgg

36

<210> SEQ ID NO 626
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 626

tgggtgcgcc agatgcccg gaaaggcctg gagtgg

36

<210> SEQ ID NO 627
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 627

tgggtgcgcc agatgcccg gaaaggcttg gagtgg

36

<210> SEQ ID NO 628
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 628

tgggtgcgcc agatgcccg gaaaggcctg gagtgg

36

<210> SEQ ID NO 629
<211> LENGTH: 36
<212> TYPE: DNA

-continued

<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 629

tgggtgcgcc agatgcccg gaaagaactg gagtgg

36

<210> SEQ ID NO 630
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 630

tggatcaggc agtccccatc gagaggcctt gagtgg

36

<210> SEQ ID NO 631
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 631

tgcgacaggc ccctggacaa gggcttgagt ggatgg

36

<210> SEQ ID NO 632
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 632

tgggtatgtt agaccctgg acagggtttt gagtgg

36

<210> SEQ ID NO 633
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHV primer

<400> SEQUENCE: 633

tgggtgcac aggccctgg acaagggttt gagtgg

36

<210> SEQ ID NO 634
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

-continued

```

<220> FEATURE:
<223> OTHER INFORMATION: TCR gamma primer

<400> SEQUENCE: 634
atcacgagtg ttgttccact gccaaagagt ttc                                33

<210> SEQ ID NO 635
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: TCR gamma primer

<400> SEQUENCE: 635
atcacgagct ttgttccggg accaaataacc ttg                                33

<210> SEQ ID NO 636
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: TCR gamma primer

<400> SEQUENCE: 636
atcacgctta gtcccttcag caaatatctt gaa                                33

<210> SEQ ID NO 637
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: TCR gamma primer

<400> SEQUENCE: 637
atcacgccta gtccctttt caaacgtttt gat                                33

<210> SEQ ID NO 638
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHJ primer

<400> SEQUENCE: 638
gctccccgct atccccagac agcagac                                27

<210> SEQ ID NO 639
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHJ primer

<400> SEQUENCE: 639

```

-continued

agactgggag ggggctgcag tgggact

27

```

<210> SEQ_ID NO 640
<211> LENGTH: 28
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHJ primer

<400> SEQUENCE: 640

```

agagaaaaggaa ggcagaagga aagccatc

28

```

<210> SEQ_ID NO 641
<211> LENGTH: 28
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHJ primer

<400> SEQUENCE: 641

```

cttcagagtt aaagcaggag agaggttg

28

```

<210> SEQ_ID NO 642
<211> LENGTH: 28
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHJ primer

<400> SEQUENCE: 642

```

tccctaagtg gactcagaga gggggtgtgg

28

```

<210> SEQ_ID NO 643
<211> LENGTH: 28
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: IGHJ primer

<400> SEQUENCE: 643

```

aaaaacaaag gcccttagagt ggccattc

28

```

<210> SEQ_ID NO 644
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV25-1 primer

<400> SEQUENCE: 644

```

ggagatcttt cctctgagtc aacagtctcc agaata

36

-continued

<210> SEQ ID NO 645
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV12-1 primer

<400> SEQUENCE: 645

ggattgattc tcagcacaga tgcctgatgt

30

<210> SEQ ID NO 646
<211> LENGTH: 32
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV12-5 primer

<400> SEQUENCE: 646

gattctcagc agagatgcct gatgcaactt ta

32

<210> SEQ ID NO 647
<211> LENGTH: 41
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV2 primer

<400> SEQUENCE: 647

aagtctgaaa tattcgatga tcaattctca gttgaaaggc c

41

<210> SEQ ID NO 648
<211> LENGTH: 26
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV16 primer

<400> SEQUENCE: 648

agctaagtgc ctcccaaatt caccct

26

<210> SEQ ID NO 649
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV5-1 primer

<400> SEQUENCE: 649

cgattctcag ggcgccagtt ctcta

25

<210> SEQ ID NO 650
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence

-continued

<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV14 primer

<400> SEQUENCE: 650

tcttagctga aaggactgga gggacgtat

29

<210> SEQ ID NO 651
<211> LENGTH: 32
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV12-4 primer

<400> SEQUENCE: 651

gaggatcgat ttcagctaa gatgcctaat gc

32

<210> SEQ ID NO 652
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV28 primer

<400> SEQUENCE: 652

tcctgagggg tacagtgtct ctagagaga

29

<210> SEQ ID NO 653
<211> LENGTH: 34
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV27 primer

<400> SEQUENCE: 653

gatgttcctg aagggtacaa agtctctcga aaag

34

<210> SEQ ID NO 654
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV5-4 primer

<400> SEQUENCE: 654

ctccttagatt ctcaggtctc cagttcccta

30

<210> SEQ ID NO 655
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
primer
<220> FEATURE:

-continued

<223> OTHER INFORMATION: TRBV7-1 primer

<400> SEQUENCE: 655

cgtgatcggt tctctgcaca gaggt

<210> SEQ ID NO 656

<211> LENGTH: 25

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<220> FEATURE:

<223> OTHER INFORMATION: TRBV19 primer

<400> SEQUENCE: 656

gctgaagggt acagcgtctc tcggg

<210> SEQ ID NO 657

<211> LENGTH: 25

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<220> FEATURE:

<223> OTHER INFORMATION: TRBV5-3 primer

<400> SEQUENCE: 657

cgattctcag ggcgccagtt ccatg

<210> SEQ ID NO 658

<211> LENGTH: 33

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<220> FEATURE:

<223> OTHER INFORMATION: TRBV9 primer

<400> SEQUENCE: 658

caacagttcc ctgacttgca ctctgaacta aac

<210> SEQ ID NO 659

<211> LENGTH: 33

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<220> FEATURE:

<223> OTHER INFORMATION: TRBV6-7 primer

<400> SEQUENCE: 659

agaagttccc aatggctaca atgtctccag atc

<210> SEQ ID NO 660

<211> LENGTH: 31

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<220> FEATURE:

<223> OTHER INFORMATION: TRBV6-4 primer

<400> SEQUENCE: 660

-continued

aagtccctga tggttatagt gtctccagag c 31

<210> SEQ ID NO 661
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV6-1 primer

<400> SEQUENCE: 661

gtccccaatg gctacaatgt ctccagatt 29

<210> SEQ ID NO 662
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV7-9 primer

<400> SEQUENCE: 662

ttctctgcag agaggcctaa gggatct 27

<210> SEQ ID NO 663
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV7-3 primer

<400> SEQUENCE: 663

gcccaacgat cggttcttgc cagt 24

<210> SEQ ID NO 664
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV7-4 primer

<400> SEQUENCE: 664

ccagtggtcg gttctctgca gag 23

<210> SEQ ID NO 665
<211> LENGTH: 28
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV5-6 primer

<400> SEQUENCE: 665

gcaactcccc tgatcgattc tcaggtca 28

<210> SEQ ID NO 666

-continued

<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV5-8 primer

<400> SEQUENCE: 666

cagagggaaac ttccctccta gatttcagg tcg

33

<210> SEQ ID NO 667
<211> LENGTH: 26
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV7-8 primer

<400> SEQUENCE: 667

gccccagtgtat cgcttctttg cagaaa

26

<210> SEQ ID NO 668
<211> LENGTH: 26
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV12-2 primer

<400> SEQUENCE: 668

cgatttcag ctgagaggcc tcatgg

26

<210> SEQ ID NO 669
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV15 primer

<400> SEQUENCE: 669

aggccgaaca cttctttctg ctttcttgac

30

<210> SEQ ID NO 670
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV6-2 primer

<400> SEQUENCE: 670

caaaggagag gtccctgatg gctacaa

27

<210> SEQ ID NO 671
<211> LENGTH: 28
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

-continued

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV23-1 primer

<400> SEQUENCE: 671

gattctcatc tcaatgcccc aagaacgc

28

<210> SEQ ID NO 672
<211> LENGTH: 31
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV10-2 primer

<400> SEQUENCE: 672

cagataaaagg agaagtcccc gatggctatg t

31

<210> SEQ ID NO 673
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV30 primer

<400> SEQUENCE: 673

caggaccggc agttcatcct gagt

24

<210> SEQ ID NO 674
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV10-3 primer

<400> SEQUENCE: 674

agataactgac aaaggagaag tctcagatgg ctatag

36

<210> SEQ ID NO 675
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV6-6 primer

<400> SEQUENCE: 675

gacaaaaggag aagtcccgaa tggctacaac

30

<210> SEQ ID NO 676
<211> LENGTH: 31
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV13 primer

-continued

<400> SEQUENCE: 676

ccctgatcga ttctcagctc aacagttcag t

31

<210> SEQ ID NO 677
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV4-1 primer

<400> SEQUENCE: 677

cctgaatgcc ccaacagctc tctcttaaac

30

<210> SEQ ID NO 678
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV4-3 primer

<400> SEQUENCE: 678

cctgaatgcc ccaacagctc tcacttattc

30

<210> SEQ ID NO 679
<211> LENGTH: 37
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV26 primer

<400> SEQUENCE: 679

ggagatgtct ctgagaggta tcatgtttct tgaaata

37

<210> SEQ ID NO 680
<211> LENGTH: 37
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV6-8 primer

<400> SEQUENCE: 680

tacaatgtct ctagattaaa cacagaggat ttccccac

37

<210> SEQ ID NO 681
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV3-2 primer

<400> SEQUENCE: 681

ttctcacctg actctccaga caaaagctcat

30

-continued

<210> SEQ ID NO 682
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV11-2 primer

<400> SEQUENCE: 682

cctaaggatc gattttctgc agagaggctc

30

<210> SEQ ID NO 683
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV2 primer

<400> SEQUENCE: 683

cctgaatgcc ctgacagctc tcgcttata

29

<210> SEQ ID NO 684
<211> LENGTH: 37
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV3-1 primer

<400> SEQUENCE: 684

gcttctcacc taaatctcca gacaaagctc acttaaa

37

<210> SEQ ID NO 685
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV29-1 primer

<400> SEQUENCE: 685

catcagccgc ccaaaccctaa cattctcaa

29

<210> SEQ ID NO 686
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV18 primer

<400> SEQUENCE: 686

attttctgct gaatttccca aagaggggcc

29

<210> SEQ ID NO 687
<211> LENGTH: 29

-continued

<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV17 primer

<400> SEQUENCE: 687

attcacagct gaaagaccta acggaacgt

29

<210> SEQ ID NO 688
<211> LENGTH: 26
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV20-1 primer

<400> SEQUENCE: 688

caagcctgac cttgtccact ctgaca

26

<210> SEQ ID NO 689
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV7-6 primer

<400> SEQUENCE: 689

ggttctctgc agagaggcct gagg

24

<210> SEQ ID NO 690
<211> LENGTH: 34
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV24-1 primer

<400> SEQUENCE: 690

gagagatctc tcatggatac agtgtcttc gaca

34

<210> SEQ ID NO 691
<211> LENGTH: 26
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV7-2 primer

<400> SEQUENCE: 691

gatcgcttct ctgcagagag gactgg

26

<210> SEQ ID NO 692
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic

-continued

```

primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV6-9 primer

<400> SEQUENCE: 692
aaggagaagt ccccgatggc tacaatgtt 29

<210> SEQ ID NO 693
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV6-5 primer

<400> SEQUENCE: 693
aaggagaagt ccccaatggc tacaatgtt 29

<210> SEQ ID NO 694
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV5-5 primer

<400> SEQUENCE: 694
aagagggaaac ttccctgatc gattctcagg 30

<210> SEQ ID NO 695
<211> LENGTH: 35
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBV10-1 primer

<400> SEQUENCE: 695
gacactaaca aaggagaagt ctcagatggc tacag 35

<210> SEQ ID NO 696
<211> LENGTH: 35
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBJ1-1 primer

<400> SEQUENCE: 696
ttacctacaa ctgtgagtc ggtgccttgtt ccaaa 35

<210> SEQ ID NO 697
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBJ1-2 primer

```

-continued

<400> SEQUENCE: 697

tacaacggtt aacctgggcc ccgaaccgaa

30

<210> SEQ ID NO 698
<211> LENGTH: 34
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBJ1-3 primer

<400> SEQUENCE: 698

acctacaaca gtgagccaaac ttccctctcc aaaa

34

<210> SEQ ID NO 699
<211> LENGTH: 31
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBJ1-4 primer

<400> SEQUENCE: 699

caagacagag agctgggttc cactgc当地 a

31

<210> SEQ ID NO 700
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBJ1-5 primer

<400> SEQUENCE: 700

accttagatg gagatcgag tccccatcacc aaa

33

<210> SEQ ID NO 701
<211> LENGTH: 28
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBJ1-6 primer

<400> SEQUENCE: 701

tcacagttag octgggtcccg ttcccaaa

28

<210> SEQ ID NO 702
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBJ2-1 primer

<400> SEQUENCE: 702

cggtgagccg tgtccctggc ccgaa

25

-continued

<210> SEQ ID NO 703
<211> LENGTH: 31
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBJ2-2 primer

<400> SEQUENCE: 703

ccagtacggc cagcctagag ctttctccaa a

31

<210> SEQ ID NO 704
<211> LENGTH: 26
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBJ2-3 primer

<400> SEQUENCE: 704

actgtcagcc gggtgcctgg gccaaa

26

<210> SEQ ID NO 705
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBJ2-4 primer

<400> SEQUENCE: 705

agagccgggt cccggcgccg aa

22

<210> SEQ ID NO 706
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBJ2-5 primer

<400> SEQUENCE: 706

ggagccgcgt gcctggcccg aa

22

<210> SEQ ID NO 707
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBJ2-6 primer

<400> SEQUENCE: 707

gtcagcctgc tgccggcccc gaa

23

<210> SEQ ID NO 708
<211> LENGTH: 23
<212> TYPE: DNA

-continued

<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: TRBJ2-7 primer

<400> SEQUENCE: 708

gtgagcctgg tgccggccc gaa

23

<210> SEQ ID NO 709
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: TCRBV01p probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB-NFQ

<400> SEQUENCE: 709

actgcagcaa gaagactca ct

22

<210> SEQ ID NO 710
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: TCRBV02 probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB-NFQ

<400> SEQUENCE: 710

aagatccggt ccacaaaagct

20

<210> SEQ ID NO 711
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: TCRBV03-1 probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB-NFQ

<400> SEQUENCE: 711

aattccctgg agcttggta ct

22

<210> SEQ ID NO 712
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: TCRBV03-2p probe
<220> FEATURE:

-continued

<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB-NFQ
<400> SEQUENCE: 712

aattccctgg agcttggta ct

22

<210> SEQ ID NO 713
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: TCRBV04-1 probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB-NFQ
<400> SEQUENCE: 713

cagaagactc agccctgtat ct

22

<210> SEQ ID NO 714
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: TCRBV04-2 probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB-NFQ
<400> SEQUENCE: 714

agaagactcg gccctgtatc t

21

<210> SEQ ID NO 715
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: TCRBV04-3 probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB-NFQ
<400> SEQUENCE: 715

agaagactcg gccctgtatc t

21

<210> SEQ ID NO 716
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: TCRBV05-1 probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB-NFQ

-continued

<400> SEQUENCE: 716

aatgtgagca ccttggagct

20

<210> SEQ ID NO 717
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: TCRBV05-2p probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB-NFQ

<400> SEQUENCE: 717

actgagtcaa acacggagct

20

<210> SEQ ID NO 718
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: TCRBV05-3 probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB-NFQ

<400> SEQUENCE: 718

aatgtgagtg ccttggagct

20

<210> SEQ ID NO 719
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: TCRBV05-4 probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB-NFQ

<400> SEQUENCE: 719

aatgtgaacg ccttggagct

20

<210> SEQ ID NO 720
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: TCRBV05-5 probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB-NFQ

<400> SEQUENCE: 720

-continued

tgtgaacgcc ttgttgct

18

<210> SEQ ID NO 721
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: TCRBV05-6 probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB-NFQ

<400> SEQUENCE: 721

tgtgaacgcc ttgttgct

18

<210> SEQ ID NO 722
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: TCRBV05-7 probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB-NFQ

<400> SEQUENCE: 722

tgtgaacgcc ttgttgct

18

<210> SEQ ID NO 723
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: TCRBV05-8 probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB-NFQ

<400> SEQUENCE: 723

tgtgaacgcc ttgttgct

18

<210> SEQ ID NO 724
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: TCRBV06-1 probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB-NFQ

<400> SEQUENCE: 724

cctcccaagac atctgtgtac tt

22

-continued

<210> SEQ_ID NO 725
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: TCRBV06-2 probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB-NFQ

<400> SEQUENCE: 725

tccctcccaa acatctgtgt

20

<210> SEQ_ID NO 726
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: TCRBV06-3 probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB-NFQ

<400> SEQUENCE: 726

tccctcccaa acatctgtgt

20

<210> SEQ_ID NO 727
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: TCRBV06-4 probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB-NFQ

<400> SEQUENCE: 727

tgctgtaccc tctcagacat ct

22

<210> SEQ_ID NO 728
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: TCRBV06-5 probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB-NFQ

<400> SEQUENCE: 728

cctcccagac atctgtgtac tt

22

<210> SEQ_ID NO 729
<211> LENGTH: 22
<212> TYPE: DNA

-continued

<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: TCRBV06-6 probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB-NFQ

<400> SEQUENCE: 729

cctcccaagac atctgtgtac tt

22

<210> SEQ ID NO 730
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: TCRBV06-7 probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB-NFQ

<400> SEQUENCE: 730

tgctccctct cagacttctg tt

22

<210> SEQ ID NO 731
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: TCRBV06-8 probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB-NFQ

<400> SEQUENCE: 731

cctcccaagac atctgtgtac tt

22

<210> SEQ ID NO 732
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: TCRBV06-9 probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB-NFQ

<400> SEQUENCE: 732

tccctccccag acatctgtat

20

<210> SEQ ID NO 733
<211> LENGTH: 17
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic

-continued

```

probe
<220> FEATURE:
<223> OTHER INFORMATION: TCRBV07-1 probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB-NFQ

<400> SEQUENCE: 733

```

aagtccagc gcacaca

17

```

<210> SEQ ID NO 734
<211> LENGTH: 17
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      probe
<220> FEATURE:
<223> OTHER INFORMATION: TCRBV07-2 probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB-NFQ

<400> SEQUENCE: 734

```

atccagcgca cacagca

17

```

<210> SEQ ID NO 735
<211> LENGTH: 17
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      probe
<220> FEATURE:
<223> OTHER INFORMATION: TCRBV07-3 probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB-NFQ

<400> SEQUENCE: 735

```

aagatccagc gcacaga

17

```

<210> SEQ ID NO 736
<211> LENGTH: 17
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      probe
<220> FEATURE:
<223> OTHER INFORMATION: TCRBV07-4 probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB-NFQ

<400> SEQUENCE: 736

```

aagatccagc gcacaga

17

```

<210> SEQ ID NO 737
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      probe
<220> FEATURE:
<223> OTHER INFORMATION: TCRBV07-5p probe

```

-continued

<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB-NFQ

<400> SEQUENCE: 737

atccagcgca cagagcaa

18

<210> SEQ ID NO 738
<211> LENGTH: 17
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: TCRBV07-6 probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB-NFQ

<400> SEQUENCE: 738

atccagcgca cagagca

17

<210> SEQ ID NO 739
<211> LENGTH: 17
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: TCRBV07-7 probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB-NFQ

<400> SEQUENCE: 739

atccagcgca cagagca

17

<210> SEQ ID NO 740
<211> LENGTH: 17
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: TCRBV07-8 probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB-NFQ

<400> SEQUENCE: 740

aagatccagc gcacaca

17

<210> SEQ ID NO 741
<211> LENGTH: 17
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: TCRBV07-9 probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:

-continued

<223> OTHER INFORMATION: 3' MGB-NFQ

<400> SEQUENCE: 741

atccagcgca cagagca

17

<210> SEQ ID NO 742
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: TCRBV08-1p probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB-NFQ

<400> SEQUENCE: 742

aacccctggag tctactagca

20

<210> SEQ ID NO 743
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: TCRBV08-2p probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB-NFQ

<400> SEQUENCE: 743

agccagacct atctgtacca

20

<210> SEQ ID NO 744
<211> LENGTH: 16
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: TCRBV09 probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB-NFQ

<400> SEQUENCE: 744

agctctctgg agctgg

16

<210> SEQ ID NO 745
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: TCRBV10-1 probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB-NFQ

<400> SEQUENCE: 745

-continued

cctcctccca gacatctgtta ta 22

```

<210> SEQ ID NO 746
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      probe
<220> FEATURE:
<223> OTHER INFORMATION: TCRBV10-2 probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB-NFQ

```

<400> SEQUENCE: 746

cgctcccaga catctgtgtta tt 22

```

<210> SEQ ID NO 747
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      probe
<220> FEATURE:
<223> OTHER INFORMATION: TCRBV10-3 probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB-NFQ

```

<400> SEQUENCE: 747

agctcccaga catctgtgtta ct 22

```

<210> SEQ ID NO 748
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      probe
<220> FEATURE:
<223> OTHER INFORMATION: TCRBV11-1 probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB-NFQ

```

<400> SEQUENCE: 748

aagatccagc ctgcagagct t 21

```

<210> SEQ ID NO 749
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      probe
<220> FEATURE:
<223> OTHER INFORMATION: TCRBV11-2 probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB-NFQ

```

<400> SEQUENCE: 749

atccagcctg caaagcttga 20

-continued

<210> SEQ ID NO 750
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: TCRBV11-3 probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB-NFQ

<400> SEQUENCE: 750

aagatccagc ctgcagagct t

21

<210> SEQ ID NO 751
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: TCRBV12-1p probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB-NFQ

<400> SEQUENCE: 751

ccagggactt gggcctataat tt

22

<210> SEQ ID NO 752
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: TCRBV12-2p probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB-NFQ

<400> SEQUENCE: 752

aagatccagc ctgcagagca

20

<210> SEQ ID NO 753
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: TCRBV12-3 probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB-NFQ

<400> SEQUENCE: 753

agggactcag ctgtgtactt

20

<210> SEQ ID NO 754
<211> LENGTH: 20

-continued

<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: TCRBV12-4 probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB-NFQ

<400> SEQUENCE: 754

agggactcag ctgtgtactt

20

<210> SEQ ID NO 755
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: TCRBV12-5 probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB-NFQ

<400> SEQUENCE: 755

ccagggactc agctgtgtat tt

22

<210> SEQ ID NO 756
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: TCRBV13 probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB-NFQ

<400> SEQUENCE: 756

aacatgagct ctttgagct

20

<210> SEQ ID NO 757
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: TCRBV14 probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB-NFQ

<400> SEQUENCE: 757

tgcagaactg gaggattctg ga

22

<210> SEQ ID NO 758
<211> LENGTH: 16
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

-continued

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: TCRBV15 probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB-NFQ
<400> SEQUENCE: 758

acgcagccat gtacct

16

<210> SEQ ID NO 759
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: TCRBV16 probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB-NFQ
<400> SEQUENCE: 759

atccaggcta cgaaggcttga

20

<210> SEQ ID NO 760
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: TCRBV17p probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB-NFQ
<400> SEQUENCE: 760

agggactcag ccgtgttatct

20

<210> SEQ ID NO 761
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: TCRBV18 probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB-NFQ
<400> SEQUENCE: 761

cgaggagatt cggcagctta tt

22

<210> SEQ ID NO 762
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:

-continued

<223> OTHER INFORMATION: TCRBV19 probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB-NFQ

<400> SEQUENCE: 762

agaaccgcac agctttct

18

<210> SEQ ID NO 763
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: TCRBV20-1 probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB-NFQ

<400> SEQUENCE: 763

tcctgaagac agcagttct

20

<210> SEQ ID NO 764
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: TCRBV21-1p probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB-NFQ

<400> SEQUENCE: 764

agatccagtc cacggagtca

20

<210> SEQ ID NO 765
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: TCRBV22p probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB-NFQ

<400> SEQUENCE: 765

acaccagcca aacagctt

18

<210> SEQ ID NO 766
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: TCRBV23-1p probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM

-continued

<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB-NFQ

<400> SEQUENCE: 766

ggcaatcctg tcctcagaa

19

<210> SEQ ID NO 767
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: TCRBV24-1 probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB-NFQ

<400> SEQUENCE: 767

cccaaccaga cagctttta ct

22

<210> SEQ ID NO 768
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: TCRBV25-1 probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB-NFQ

<400> SEQUENCE: 768

cctcacatac ctctcagtac ct

22

<210> SEQ ID NO 769
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: TCRBV26p probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB-NFQ

<400> SEQUENCE: 769

agcaccaacc agacatctgt

20

<210> SEQ ID NO 770
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: TCRBV27-1 probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB-NFQ

-continued

<400> SEQUENCE: 770

ccaaaccagac ctctctgtac tt

22

<210> SEQ ID NO 771
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: TCRBV28 probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB-NFQ

<400> SEQUENCE: 771

agcaccaacc agacatct

18

<210> SEQ ID NO 772
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: TCRBV29-1 probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB-NFQ

<400> SEQUENCE: 772

tgagcaacat gagccctgaa

20

<210> SEQ ID NO 773
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: TCRBV30 probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB-NFQ

<400> SEQUENCE: 773

tccttctcag tgactctggc tt

22

<210> SEQ ID NO 774
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 774

tccggtccac aaagctggag

20

<210> SEQ ID NO 775
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence

-continued

<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 775

ctggagcttg gtgactctgc

20

<210> SEQ ID NO 776
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 776

ccctgtatct ctgcgccage

20

<210> SEQ ID NO 777
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 777

ttggagctgg gggactcg

18

<210> SEQ ID NO 778
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: 5' FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB

<400> SEQUENCE: 778

ttagctgaat gtgaacgcct t

21

<210> SEQ ID NO 779
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 779

tctgtgtact tctgtgccag ca

22

<210> SEQ ID NO 780
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 780

agctgctccc tctcagactt

20

<210> SEQ ID NO 781

-continued

<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 781

tgctccctcc cagacatctg

20

<210> SEQ ID NO 782
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 782

tctgaaggtc cagcgcacac

20

<210> SEQ ID NO 783
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 783

ctgtgccagc agcttagc

18

<210> SEQ ID NO 784
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 784

aagatccagc gcacagagc

19

<210> SEQ ID NO 785
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 785

tttgtatttc tgtgccagca gc

22

<210> SEQ ID NO 786
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 786

tctgcgcagg cagtggat

18

<210> SEQ ID NO 787
<211> LENGTH: 20

-continued

<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB

<400> SEQUENCE: 787

tcactctgga gtccgctacc

20

<210> SEQ ID NO 788
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB

<400> SEQUENCE: 788

agtagactcc actctcaaga tcca

24

<210> SEQ ID NO 789
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 789

tttctgtgcc agcagcttg

20

<210> SEQ ID NO 790
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 790

tcggccgtgt atgtctgt

19

<210> SEQ ID NO 791
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB

<400> SEQUENCE: 791

atccagccct cagaacccag

20

<210> SEQ ID NO 792
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence

-continued

<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB

<400> SEQUENCE: 792

acatgagctc cttggagctg

20

<210> SEQ ID NO 793
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB

<400> SEQUENCE: 793

tgcagaactg gaggattctg g

21

<210> SEQ ID NO 794
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB

<400> SEQUENCE: 794

tgtacctgtg tgccaccagc

20

<210> SEQ ID NO 795
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
primer

<400> SEQUENCE: 795

tttgtccag cagccaatc

19

<210> SEQ ID NO 796
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB

<400> SEQUENCE: 796

atccagcagg tagtgcgagg

20

<210> SEQ ID NO 797
<211> LENGTH: 19

-continued

<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB

<400> SEQUENCE: 797

cactgtgaca tcggcccaa

19

<210> SEQ ID NO 798
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB

<400> SEQUENCE: 798

cagtgcocat octgaagaca

20

<210> SEQ ID NO 799
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 799

agcctggcaa tcctgtcctc

20

<210> SEQ ID NO 800
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB

<400> SEQUENCE: 800

tgtccctaga gtctgccatc c

21

<210> SEQ ID NO 801
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB

<400> SEQUENCE: 801

caggccctca cataacctctc

20

-continued

```

<210> SEQ ID NO 802
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer

```

<400> SEQUENCE: 802

tctctgtact tctgtgccag c

21

```

<210> SEQ ID NO 803
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer

```

<400> SEQUENCE: 803

ccagcaccaa ccagacatct

20

```

<210> SEQ ID NO 804
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB

```

<400> SEQUENCE: 804

tgtgagcaac atgagccctg

20

```

<210> SEQ ID NO 805
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer

```

<400> SEQUENCE: 805

tggcttctat ctctgtgcct g

21

```

<210> SEQ ID NO 806
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer

```

<400> SEQUENCE: 806

ccctgcagcc agaagact

18

```

<210> SEQ ID NO 807
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer

```

<400> SEQUENCE: 807

459

-continued

tgccgcagca gcttg

15

```

<210> SEQ ID NO 808
<211> LENGTH: 17
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer

<400> SEQUENCE: 808

```

agtgccttgg agctggg

17

```

<210> SEQ ID NO 809
<211> LENGTH: 16
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      probe

<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB

<400> SEQUENCE: 809

```

tggaggcgc tgctcc

16

```

<210> SEQ ID NO 810
<211> LENGTH: 16
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer

<400> SEQUENCE: 810

```

tcacgttggc gtctgc

16

```

<210> SEQ ID NO 811
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      probe

<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB

<400> SEQUENCE: 811

```

tgctccctcc cagacatc

18

```

<210> SEQ ID NO 812
<211> LENGTH: 16
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer

<400> SEQUENCE: 812

```

ccagcgcaca cagcag

16

```

<210> SEQ ID NO 813
<211> LENGTH: 18
<212> TYPE: DNA

```

-continued

<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 813

agatccagcg cacagacg

18

<210> SEQ ID NO 814
<211> LENGTH: 16
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 814

cagcgcacag agcagc

16

<210> SEQ ID NO 815
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB

<400> SEQUENCE: 815

ttagctctct ggagctgg

18

<210> SEQ ID NO 816
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB

<400> SEQUENCE: 816

ccttgagatc caggctacg

19

<210> SEQ ID NO 817
<211> LENGTH: 17
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 817

ttccccctgac cctggag

17

<210> SEQ ID NO 818
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM

-continued

<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB

<400> SEQUENCE: 818

tggagtcgcc cagcc

15

<210> SEQ ID NO 819
<211> LENGTH: 17
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB
<400> SEQUENCE: 819

aggagcgctt ctccccgt

17

<210> SEQ ID NO 820
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB
<400> SEQUENCE: 820

tccttctcag tgactctggc

20

<210> SEQ ID NO 821
<211> LENGTH: 17
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB
<400> SEQUENCE: 821

agcacaccttgg agctggg

17

<210> SEQ ID NO 822
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB
<400> SEQUENCE: 822

tgagtgcctt ggagctgg

18

<210> SEQ ID NO 823
<211> LENGTH: 18
<212> TYPE: DNA

-continued

<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB
<400> SEQUENCE: 823

ctggagtcag ctgctccc

18

<210> SEQ ID NO 824
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB
<400> SEQUENCE: 824

actctgaaga tccagcgca

19

<210> SEQ ID NO 825
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<400> SEQUENCE: 825

tccatctcca ctctgacga

19

<210> SEQ ID NO 826
<211> LENGTH: 16
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<400> SEQUENCE: 826

tctgctgcct cctccc

16

<210> SEQ ID NO 827
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<400> SEQUENCE: 827

attccccct cactctgg

18

<210> SEQ ID NO 828
<211> LENGTH: 16
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM

-continued

<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB

<400> SEQUENCE: 828

tccagcgac agagca

16

<210> SEQ ID NO 829
<211> LENGTH: 16
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB
<400> SEQUENCE: 829

cagcggact cagcca

16

<210> SEQ ID NO 830
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB
<400> SEQUENCE: 830

tcaaacacag aggacctccc

20

<210> SEQ ID NO 831
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB
<400> SEQUENCE: 831

cactctggag tcagctaccc

20

<210> SEQ ID NO 832
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<400> SEQUENCE: 832

ctgcagccag aagac

15

<210> SEQ ID NO 833
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

-continued

<400> SEQUENCE: 833

tcacgttggc gtctgctgta ccctc

25

<210> SEQ_ID NO 834
<211> LENGTH: 13
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 834

cagcgcacac agc

13

<210> SEQ_ID NO 835
<211> LENGTH: 17
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB

<400> SEQUENCE: 835

tcacctacac gccctgc

17

<210> SEQ_ID NO 836
<211> LENGTH: 17
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB

<400> SEQUENCE: 836

cacacaccctg cagccag

17

<210> SEQ_ID NO 837
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB

<400> SEQUENCE: 837

cacagatgtat ttccccctc

19

<210> SEQ_ID NO 838
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: 5'FAM

-continued

<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB

<400> SEQUENCE: 838

ctgaagttcc agcgacaca

18

<210> SEQ ID NO 839
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: 5' FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB
<400> SEQUENCE: 839

tccgtctcca ctctgacga

19

<210> SEQ ID NO 840
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 840

agatttggac ctgcgagc

18

<210> SEQ ID NO 841
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 841

gagcggctgt ctccacaagt

20

<210> SEQ ID NO 842
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe

<400> SEQUENCE: 842

cgcgcagag ctttc

15

<210> SEQ ID NO 843
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 843

tatagctgaa gggtagacgcg tctctcgaa

29

<210> SEQ ID NO 844
<211> LENGTH: 29

-continued

<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 844

ttcgatgatc aattctcagt tgaaaggcc

29

<210> SEQ ID NO 845
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 845

cctaaatctc cagacaaagc tcacttaaa

29

<210> SEQ ID NO 846
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 846

ctgaatgccca caacagctct ctcttaaac

29

<210> SEQ ID NO 847
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 847

ctgaatgccca caacagctct cacttattc

29

<210> SEQ ID NO 848
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 848

tggtcgattc tcagggcgcc agttctcta

29

<210> SEQ ID NO 849
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 849

taatcgattc tcagggcgcc agttccatg

29

<210> SEQ ID NO 850
<211> LENGTH: 29
<212> TYPE: DNA

-continued

<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 850

tcctagattc tcaggtctcc agttcccta

29

<210> SEQ ID NO 851
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 851

ggcaacttcc ctgatcgatt ctcaggtca

29

<210> SEQ ID NO 852
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 852

ggaaaacttcc ctcctagatt ttcaggtcg

29

<210> SEQ ID NO 853
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide Primer

<400> SEQUENCE: 853

gccaaaggag aggtccctga tggctacaa

29

<210> SEQ ID NO 854
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 854

gtccctgatg gttatagtgt ctccagagc

29

<210> SEQ ID NO 855
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 855

gttcccaatg gctacaatgt ctccagatc

29

<210> SEQ ID NO 856
<211> LENGTH: 29

-continued

<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 856

ctcttagatta aacacagagg atttccac

29

<210> SEQ ID NO 857
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 857

tccccgtgat cggttctctg cacagaggt

29

<210> SEQ ID NO 858
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 858

agtgtatcgct tctctgcaga gaggactgg

29

<210> SEQ ID NO 859
<211> LENGTH: 28
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 859

ggctgccccaa cgatcggttc tttgcagt

28

<210> SEQ ID NO 860
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 860

ggcggcccaag tggtcgggtc tctgcagag

29

<210> SEQ ID NO 861
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 861

atgatcggtt ctctgcagag aggcctgagg

30

<210> SEQ ID NO 862
<211> LENGTH: 29
<212> TYPE: DNA

-continued

<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 862

gctgcccagt gatcgcttct ttgcagaaaa

29

<210> SEQ ID NO 863
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 863

ggttctctgc agagaggcct aaggatct

29

<210> SEQ ID NO 864
<211> LENGTH: 28
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 864

gttccctgac ttgcactctg aactaac

28

<210> SEQ ID NO 865
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 865

aacaaaaggag aagtctcaga tggctacag

29

<210> SEQ ID NO 866
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 866

gataaaaggag aagtccccga tggctatgt

29

<210> SEQ ID NO 867
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide Primer

<400> SEQUENCE: 867

gacaaaaggag aagtctcaga tggctatag

29

<210> SEQ ID NO 868
<211> LENGTH: 29

-continued

<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 868

ctaaggatcg atttctgca gagaggctc

29

<210> SEQ ID NO 869
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 869

tcgattctca gctaaagatgc ctaatgc

27

<210> SEQ ID NO 870
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 870

ttctcagcag agatgcctga tgcaacttta

30

<210> SEQ ID NO 871
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 871

ctgatecgatt ctcagctaa cagttcagt

29

<210> SEQ ID NO 872
<211> LENGTH: 28
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 872

gccgaacact tctttctgct ttcttgac

28

<210> SEQ ID NO 873
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 873

ttcagctaa g tcctcccaa attcacccct

29

<210> SEQ ID NO 874
<211> LENGTH: 29
<212> TYPE: DNA

-continued

<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 874

tatagctgaa gggcacagcg tctctcgaa

29

<210> SEQ ID NO 875
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 875

atgcggcgtt gacccgtttt actctgaca

29

<210> SEQ ID NO 876
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 876

atctctgtat gatacagtgt ctctcgaca

29

<210> SEQ ID NO 877
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 877

tttcctctga gtcaaacagtc tccagaata

29

<210> SEQ ID NO 878
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 878

tcctgaaggg tacaaaagtct ctcgaaaaag

29

<210> SEQ ID NO 879
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 879

gaccggcaggaa ccggcagttt atcctgagt

29

<210> SEQ ID NO 880
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence

-continued

<220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 880

acctacaacg gttaacctgg tccccgaacc gaa

33

<210> SEQ ID NO 881
 <211> LENGTH: 33
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 881

acctacaaca gtgagccaac ttccctctcc aaa

33

<210> SEQ ID NO 882
 <211> LENGTH: 31
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 882

ccaagacaga gagctgggtt ccactgccaa a

31

<210> SEQ ID NO 883
 <211> LENGTH: 31
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 883

ctgtcacagt gagcctggtc ccgttccaa a

31

<210> SEQ ID NO 884
 <211> LENGTH: 33
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 884

acaactgtga gtctggtgcc ttgtccaaag aaa

33

<210> SEQ ID NO 885
 <211> LENGTH: 33
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 885

acaacggtta acctggtccc cgaaccgaag gtg

33

<210> SEQ ID NO 886
 <211> LENGTH: 33
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:

-continued

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 886

acaacagtga gccaaattcc ctctccaaaa tat

33

<210> SEQ ID NO 887

<211> LENGTH: 33

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 887

aagacagaga gctgggttcc actgccaaaa aac

33

<210> SEQ ID NO 888

<211> LENGTH: 33

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 888

aggatggaga gtcgagtccc atcaccaaaa tgc

33

<210> SEQ ID NO 889

<211> LENGTH: 33

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 889

gtcacagtga gcctggtccc gttcccaaag tgg

33

<210> SEQ ID NO 890

<211> LENGTH: 33

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 890

agcacgggtga gccgtgtccc tggccccgaag aac

33

<210> SEQ ID NO 891

<211> LENGTH: 33

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 891

agtacgggtca gccttagagcc ttctccaaaa aac

33

<210> SEQ ID NO 892

<211> LENGTH: 33

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic

-continued

oligonucleotide

<400> SEQUENCE: 892

agcactgtca gccgggtgcc tggccaaaa tac

33

<210> SEQ ID NO 893

<211> LENGTH: 33

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 893

agcactgaga gccgggtccc ggccgcgaag tac

33

<210> SEQ ID NO 894

<211> LENGTH: 33

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 894

agcaccagga gccgcgtgcc tggcccgaaag tac

33

<210> SEQ ID NO 895

<211> LENGTH: 33

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 895

agcacggta gcctgctgcc ggccccgaaa gtc

33

<210> SEQ ID NO 896

<211> LENGTH: 33

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 896

gtgaccgtga gcctggtgcc cggcccgaaag tac

33

<210> SEQ ID NO 897

<211> LENGTH: 34

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 897

tgaggagacg gtgaccaggg ttccattggcc ccag

34

<210> SEQ ID NO 898

<211> LENGTH: 34

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

-continued

<400> SEQUENCE: 898

tgaggagacg gtgaccaggg tcccttggcc ccag

34

<210> SEQ ID NO 899
<211> LENGTH: 34
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 899

tgaggagacg gtgaccaggg ttcccttggcc ccag

34

<210> SEQ ID NO 900
<211> LENGTH: 35
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 900

ctgaagagac ggtgaccatt gtcccttggc cccag

35

<210> SEQ ID NO 901
<211> LENGTH: 35
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 901

ctgaggagac ggtgaccgtg gtcccttggc cccag

35

<210> SEQ ID NO 902
<211> LENGTH: 34
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 902

tgaggagacg gtgaccgtgg tcccttggcc ccag

34

<210> SEQ ID NO 903
<211> LENGTH: 35
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 903

ctgaggagac ggtgaccgtg gtccctttgc cccag

35

<210> SEQ ID NO 904
<211> LENGTH: 35
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

-continued

<400> SEQUENCE: 904

ctgaggagac agtgaccagg gtgccacggc cccag

35

<210> SEQ ID NO 905
<211> LENGTH: 35
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 905

ctgaggagac ggtgaccagg gttccctggc cccag

35

<210> SEQ ID NO 906
<211> LENGTH: 35
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 906

ctgaggagac ggtgaccagg gttccctggc cccag

35

<210> SEQ ID NO 907
<211> LENGTH: 35
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 907

ctgaggagac ggtgaccagg gtgccctggc cccag

35

<210> SEQ ID NO 908
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: 5' FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB

<400> SEQUENCE: 908

tccgggtccac aaagctggag

20

<210> SEQ ID NO 909
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic probe
<220> FEATURE:
<223> OTHER INFORMATION: 5' FAM
<220> FEATURE:
<223> OTHER INFORMATION: 3' MGB

<400> SEQUENCE: 909

ctggagcttg gtgactctgc

20

495

The invention claimed is:

1. A method for determining a relative quantity of tumor-infiltrating lymphocytes in a solid tumor, comprising:
 - (a) obtaining a sample comprising a solid tumor tissue;
 - (b) amplifying by PCR at least 80% of all rearranged TCR or Ig CDR3-encoding regions present in said sample using a plurality of V-segment oligonucleotide primers comprising sequences selected from the group consisting of SEQ ID NOs: 1-52, 221-238, 255-260, 262-267, 269, 272, 283, 286, 291, 292, 294-297, 301-326, 330, 338, 382, 405, 447-484, 644-695, and 843-879 and a plurality of J-segment oligonucleotide primers comprising sequences selected from the group consisting of 53-63, 65, 215-220, and 247 to produce a plurality of rearranged DNA amplicons;
 - (c) amplifying by PCR a control sequence present in said sample using a pair of control sequence primers, wherein said control sequence primers are capable of amplifying a control sequence that is not an adaptive immune receptor gene and present in all cells in said sample;
 - (d) quantifying a number of adaptive immune receptor sequence reads in said sample generated from high-throughput sequencing (HTS) of said plurality of rearranged DNA amplicons;
 - (e) quantifying a number of control sequence reads in said sample using said amplified control sequence; and
 - (f) comparing said number of adaptive immune receptor sequence reads and said number of control sequence reads to estimate a relative quantity of tumor-infiltrating lymphocytes in said solid tumor.
2. The method of claim 1, further comprising quantifying a number of unique sequence reads generated from said HTS, wherein each unique sequence read comprises a sequence distinct from the other sequence reads.
3. The method of claim 1, wherein said number of control sequence reads represents a total number of diploid genomes in said sample.
4. The method of claim 3, wherein said comparing comprises dividing said number of control sequence reads in half and determining a ratio between said number of adaptive immune receptor sequence reads and half of said number of control sequence reads.
5. The method of claim 1, wherein said comparing comprises estimating a total number of adaptive immune cells in said sample by dividing said number of adaptive immune receptor sequence reads by a numerical factor.
6. The method of claim 1, wherein said plurality of rearranged DNA amplicons comprises at least 10^6 DNA molecules.
7. The method of claim 1, wherein said plurality of rearranged DNA amplicons comprises at least 10^5 DNA molecules.
8. The method of claim 1, wherein each V-segment oligonucleotide primer comprises a nucleotide sequence of at least 15 contiguous nucleotides that is complementary to at least one functional TCR or Ig V-encoding gene segment, and wherein said V-segment oligonucleotide primers specifically hybridize to at least 80% of all functional TCR or Ig V-encoding gene segments that are present in said sample.
9. The method of claim 1, wherein each J-segment oligonucleotide primer comprises a nucleotide sequence of at least 15 contiguous nucleotides that is complementary to at least one functional TCR or Ig J-encoding gene segment, and wherein said J-segment oligonucleotide primers specifically hybridize to at least 80% of all functional TCR or Ig J-encoding gene segments that are present in said test sample.

496

10. The method of claim 1, wherein each amplified rearranged TCR or Ig CDR3-encoding region is less than 600 nucleotides in length.
11. The method of claim 1, wherein each of said rearranged TCR or Ig CDR3-encoding regions encode a T cell receptor (TCR) V-region polypeptide or an immunoglobulin (Ig) V-region polypeptide comprising a V gene recombination signal sequence (RSS) and a T cell receptor (TCR) J-region polypeptide or an immunoglobulin (Ig) J-region polypeptide comprising a J gene RSS, and wherein each rearranged DNA amplicon comprises (i) at least 10, 20, 30 or 40 contiguous nucleotides of a sense strand of a TCR or Ig V-encoding gene segment, said at least 10, 20, 30 or 40 contiguous nucleotides being situated 5' to said V gene RSS and (ii) at least 10, 20 or 30 contiguous nucleotides of a sense strand of a TCR or Ig J-encoding gene segment, said at least 10, 20 or 30 contiguous nucleotides being situated 3' to said J gene RSS.
12. The method of claim 1, wherein said tumor-infiltrating lymphocytes are T cells or B cells.
13. The method of claim 1, wherein said rearranged TCR or Ig CDR3-encoding regions are selected from the group consisting of rearranged TCR α CDR3-encoding regions, TCR β CDR3-encoding regions, TCR γ CDR3-encoding regions, TCR δ CDR3-encoding regions, IgH CDR3-encoding regions, Igk CDR3-encoding regions, and Ig λ CDR3-encoding regions.
14. A method for quantifying a relative representation of tumor infiltrating T cells in a solid tissue tumor sample, comprising:
 - obtaining DNA templates from said sample;
 - amplifying rearranged T cell receptor DNA molecules utilizing a plurality of V-segment oligonucleotide primers comprising sequences selected from the group consisting of SEQ ID NOs: 1-52, 221-238, 255-260, 262-267, 269, 272, 283, 286, 291, 292, 294-297, 301-326, 330, 338, 382, 405, 447-484, 644-695 and 843-879 and a plurality of J-segment oligonucleotide primers comprising sequences selected from the group consisting of 53-63, 65, 215-220, and 247 in a single multiplex PCR from said DNA templates to produce a multiplicity of amplified rearranged DNA molecules;
 - sequencing said multiplicity of amplified rearranged DNA molecules by high-throughput sequencing (HTS) to produce rearranged T cell receptor sequence reads;
 - determining a number of rearranged T cell receptor DNA molecules from said rearranged T cell receptor sequence reads, wherein said number of T cell receptor DNA molecules is proportional to a number of T cells in said sample;
 - determining a number of diploid genomes in the sample, wherein said number of diploid genomes represents a number of total cells in the sample; and
 - quantifying a ratio of the relative representation of tumor infiltrating T cells in said sample by comparing said number of T cells by said number of total cells in the sample.
15. The method of claim 14, wherein each V-segment oligonucleotide primer comprises a nucleotide sequence of at least 15 contiguous nucleotides that is complementary to at least one functional TCR V-encoding gene segment, and wherein said V-segment oligonucleotide primers specifically hybridize to at least 80% of all functional TCR V-encoding gene segments that are present in said sample.
16. The method of claim 15, wherein each J-segment oligonucleotide primer comprises a nucleotide sequence of at least 15 contiguous nucleotides that is complementary to at least one functional TCR J-encoding gene segment, and

497

wherein said J-segment oligonucleotide primers specifically hybridize to at least 80% of all functional TCR J-encoding gene segments that are present in said test sample.

17. The method of claim **14**, wherein each of said rearranged TCR encodes a T cell receptor (TCR) V-region polypeptide comprising a V gene recombination signal sequence (RSS) and a T cell receptor (TCR) J-region polypeptide comprising a J gene RSS, and wherein each rearranged DNA molecule comprises (i) at least 10, 20, 30 or 40 contiguous nucleotides of a sense strand of a TCR V-encoding gene segment, said at least 10, 20, 30 or 40 contiguous nucleotides being situated 5' to said V gene RSS and (ii) at least 10, 20 or 30 contiguous nucleotides of a sense strand of a TCR J-encoding gene segment, said at least 10, 20 or 30 contiguous nucleotides being situated 3' to said J gene RSS.

18. The method of claim **14**, wherein said number of diploid genomes in said sample is determined by contacting said sample with a pair of control sequence primers and by amplifying a control sequence from said DNA templates, wherein

498

said control sequence primers are capable of amplifying a control sequence present in all cells in said sample.

19. The method of claim **14**, further comprising quantifying a number of unique sequence reads generated from said HTS, wherein each unique sequence read comprises a sequence distinct from the other sequence reads.

20. The method of claim **14**, wherein said comparing comprises dividing said number of T cells by a numerical factor.

21. The method of claim **14**, wherein said rearranged DNA molecules are selected from the group consisting of rearranged TCR α CDR3-encoding regions, TCR β CDR3-encoding regions, TCR γ CDR3-encoding regions, and TCR δ CDR3-encoding regions.

22. The method of claim **1**, wherein the amplifying steps of (b) and (c) are performed in the same PCR reaction.

23. The method of claim **1**, wherein the amplifying steps of (b) and (c) are performed in separate PCR reactions.

* * * * *